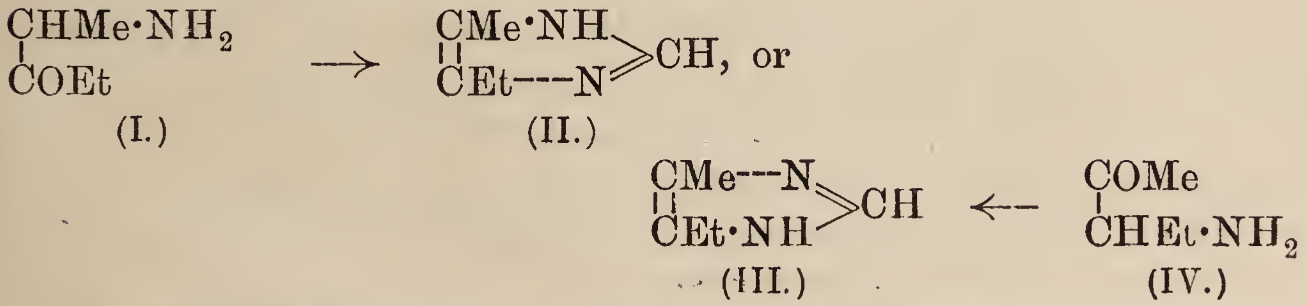
CXCV.—*The Tautomerism of Glyoxalines and the Constitution of Pilocarpine.*

By Frank Lee Pyman.

Since the suggestion of Pinner and Schwarz (*Ber.*, 1902, **35**, 2441), followed by the experimental proof adduced by Jowett (Trans., 1903, **83**, 438), that the glyoxaline radicle is contained in the alkaloid pilocarpine, and later the discovery by Pauly (*Zeitsch. physiol. Chem.*, 1904, **42**, 508) of this radicle in histidine, synthetic experiments with glyoxalines have attracted the attention of a number of chemists. Quite recently an added stimulus has been given to the work through the discovery by Barger and Dale (Proc., 1910, **26**, 128) that β-iminazolylethylamine, a compound which was recently synthesised by Windaus and Vogt (*Ber.*, 1907, **40**, 3691), is one of the active principles of ergot.

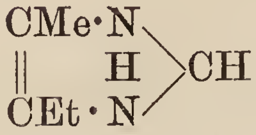
Some years ago Dr. Jowett (Jowett and Potter, Trans., 1903, **83**, 464; Jowett, Trans., 1905, **87**, 405), with a view to syntheses in this field, commenced a series of investigations, which will be referred to in detail later, and more recently, being unable to resume the work personally, requested the present author to continue it. The most important result of the present investigation is the proof that glyoxalines, containing a free imino-hydrogen atom, are tautomeric, a fact which previous research on the subject had already made probable. Thus, Jänecke (*Ber.*, 1899, **32**, 1098) prepared, by the oxidation of the mercaptan formed by the action of potassium thiocyanate on α-aminodiethyl ketone (I), the same methylethylglyoxaline (II or III) which Gabriel and Posner (*Ber.*, 1894, **27**, 1037) had previously obtained in a similar manner from α-aminopropyl methyl ketone (IV):



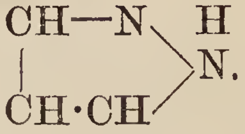
$$\underset{\text{(I.)}}{\begin{array}{l}\mathrm{CHMe\cdot NH_2}\\ \mid\\ \mathrm{COEt}\end{array}} \longrightarrow \underset{\text{(II.)}}{\begin{array}{l}\mathrm{CMe\cdot NH}\\ \parallel\\ \mathrm{CEt---N}\end{array}\!\!>\mathrm{CH}}, \text{ or}$$

$$\underset{\text{(III.)}}{\begin{array}{l}\mathrm{CMe---N}\\ \parallel\\ \mathrm{CEt\cdot NH}\end{array}\!\!>\mathrm{CH}} \longleftarrow \underset{\text{(IV.)}}{\begin{array}{l}\mathrm{COMe}\\ \mid\\ \mathrm{CHEt\cdot NH_2}\end{array}}.$$

This method of synthesis does not enable any conclusion to be drawn as to which of the two isomerides, 5-methyl-4-ethylglyoxaline (II) and 4-methyl-5-ethylglyoxaline (III), is to be expected in each case, but it was inferred that a different one of the two would be expected in the two cases; the fact that the same methylethylglyoxaline was actually obtained in each case consequently showed either that this compound is tautomeric, or that one of the two forms (II) and (III) is the more stable. Jänecke thought the former view the more probable, and suggested that the imino-hydrogen atom vibrated between the nitrogen atoms in the same way as it does, according to Knorr (*Annalen*, 1894, **279**, 188), in the case of the pyrazoles:

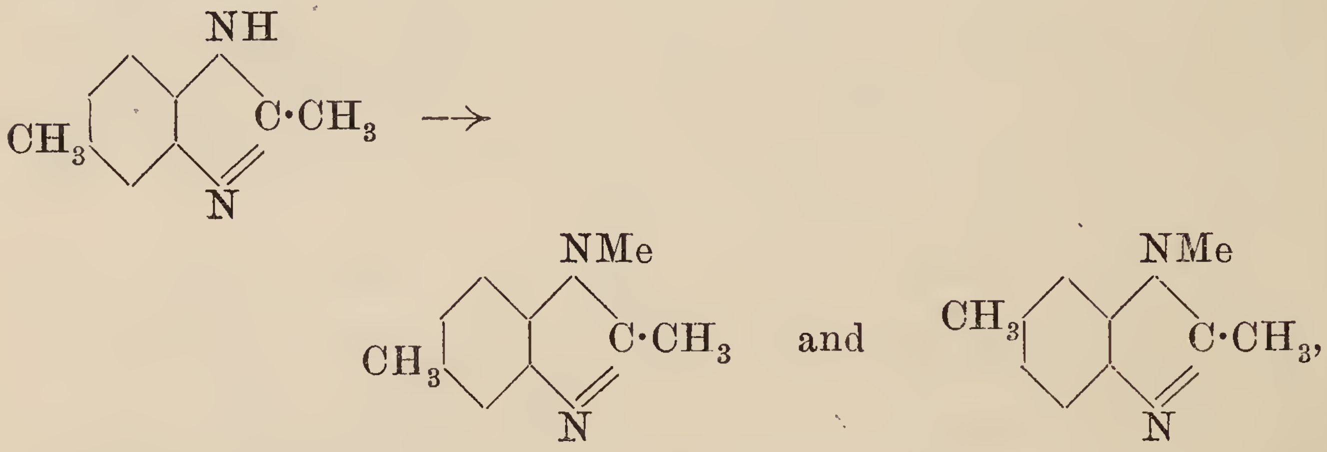


$$\begin{array}{l}\text{CMe·N}\\ \|\qquad\ \text{H}\\ \text{CEt·N}\end{array}\!\!>\text{CH}$$



$$\begin{array}{l}\text{CH—N}\quad\text{H}\\ |\\ \text{CH·CH}\end{array}\!\!>\text{N.}$$

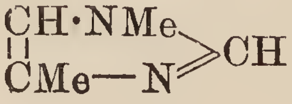
Several years later, Otto Fischer (*J. pr. Chem.*, 1906, [ii], **73**, 419; 1907, [ii], **75**, 88) prepared the 1 : 2 : 5- and 1 : 2 : 6-trimethylbenziminazoles by the action of methyl iodide on 2 : 5-dimethylbenziminazole:



and thus showed that this compound is tautomeric.

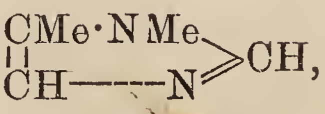
In consequence of this result, and in order to demonstrate that the simple glyoxalines are also probably tautomeric, Gabriel (*Ber.*, 1908, **41**, 1926), who appears to have overlooked Jänecke's paper, brought forward another example of the formation from two different amino-ketones of a single 4 : 5-disubstituted glyoxaline, namely, phenylmethylglyoxaline. On the other hand, neither Jowett and Potter (*loc. cit.*) in the methylation of 4(or 5)-methylglyoxaline, nor Pinner (*Ber.*, 1905, **38**, 1535) in the ethylation of 4(or 5)-phenylglyoxaline, isolated two isomeric *N*-alkyl derivatives, and further, in more recent publications, both Pauly and Gundermann (*Ber.*, 1908, **41**, 4005) and Windaus (*Ber.*, 1909, **42**, 762) describe experiments with "*α-N*-dimethyliminazol"—presumably the methylation product of *α*-methylglyoxaline, that is, 4(or 5)-methylglyoxaline. The tautomerism of glyoxalines has therefore not hitherto been generally recognised.

A definite proof of the tautomerism of simple glyoxalines is now brought forward, for it has been found that 4(or 5)-methylglyoxaline yields, on methylation, a mixture of two isomeric *N*-methyl derivatives, 1 : 4- and 1 : 5-*dimethylglyoxaline* (V and VI) respectively:



$$\begin{array}{l}\text{CH·NMe}\\ \|\\ \text{CMe—N}\end{array}\!\!\geqslant\text{CH}$$

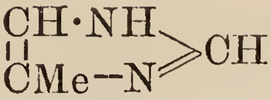
(V.)



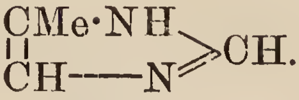
$$\begin{array}{l}\text{CMe·NMe}\\ \|\\ \text{CH——N}\end{array}\!\!\geqslant\text{CH,}$$

(VI.)

and therefore reacts according to both the formulæ (VII and VIIa):


(VII.)

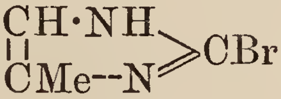
and

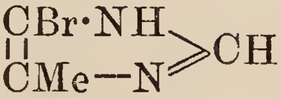

(VIIa.)

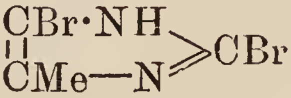
It may therefore be considered to react as a compound in which the hydrogen atom of the imino-group alternates in position between the two nitrogen atoms as suggested by Jänecke (*loc. cit.*) in the case of methylethylglyoxaline.

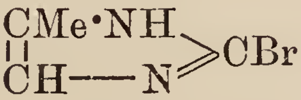
The formation of two isomeric *N*-methyl derivatives by the methylation of a glyoxaline has been confirmed by the methylation of the bromo-derivatives of 4(or 5)-methylglyoxaline.

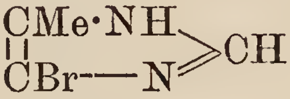
The action on 4(or 5)-methylglyoxaline of bromine in a quantity sufficient to form a monobromo-substitution product has been tried at different temperatures, and it has been found that, even at −10°, the *monobromo*-derivative is accompanied by a considerable proportion of the *dibromo*-derivative, a corresponding quantity of 4(or 5)-methylglyoxaline being consequently unattacked. Only one monobromo-derivative has been isolated, and there is at present no evidence to show whether the substituent bromine atom occupies the 2- or the 4(or 5)-position. This compound is tautomeric, and reacts either as 2-bromo-4-methylglyoxaline (VIII) and 2-bromo-5-methylglyoxaline (VIIIa) or as 5-bromo-4-methylglyoxaline (IX) and 4-bromo-5-methylglyoxaline (IXa):

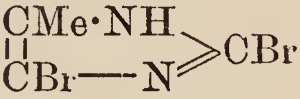

(VIII.)


(IX.)


(X.)


(VIIIa.)


(IXa.)

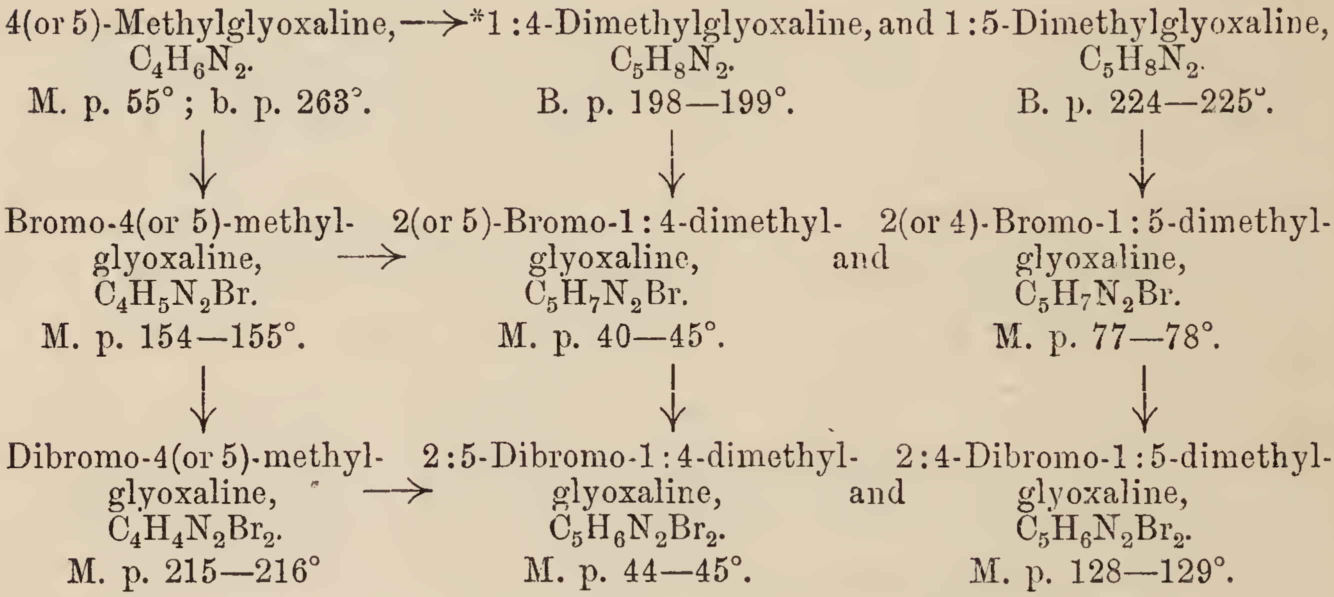

(Xa.)

The dibromo-derivative is also tautomeric, and reacts as 2:5-dibromo-4-methylglyoxaline (X) and 2:4-dibromo-5-methylglyoxaline (Xa).

Bromo-4(or 5)-methylglyoxaline yields, on methylation, a mixture of two isomeric *bromodimethylglyoxalines*, which melt at 40—45° and 77—78° respectively.

Dibromo-4(or 5)-methylglyoxaline similarly yields, on methylation, a mixture of two isomeric *dibromodimethylglyoxalines*, melting at 44—45° and 128—129°. The two dimethylglyoxalines obtained by the methylation of 4(or 5)-methylglyoxaline distil at 198—199° and 224—225°, and in order to determine which of the isomeric bromo- and dibromo-dimethylglyoxalines was derived from each dimethylglyoxaline, the latter bases were also brominated. Although the bromination of the two isomerides was carried out under precisely similar conditions, the results showed an interesting difference, the dimethylglyoxaline boiling at 198—199° yielding chiefly the corresponding monobromo-derivative which melts at 40—45°, and very little of the dibromodimethylglyoxaline which melts at 44—45°; whilst the dimethylglyoxaline boiling at 224—225° gave very little of the corresponding monobromodimethylglyoxaline melting at 77—78°, but chiefly the dibromodimethylglyoxaline melting at 128—129°.

The mutual relations between the isomeric dimethylglyoxalines and the various bromo-derivatives are shown by the following scheme:

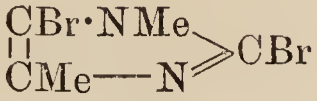


* The numbers are inserted in anticipation of the conclusions drawn later.

The question as to which series has the 1:4 and which the 1:5 arrangement of methyl groups is difficult to determine, and no direct evidence bearing on this point is brought forward at present. Fortunately, however, this matter can be settled with a high degree of probability by consideration of the relative affinities of the two dibromodimethylglyoxalines. These compounds are weak bases, and it has been found that the isomeride melting at 128—129° is very much more readily extracted by means of chloroform from its solution in 10 per cent. hydrochloric acid than the isomeride melting at 44—45°; the latter is therefore the stronger base.

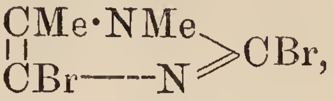
Now, of the two nitrogen atoms in the glyoxaline molecule, the iminic nitrogen atom occupies a similar position to the nitrogen atom of pyrrole, and is almost devoid of basic properties. Glyoxalines behave as mono-acid bases, and the fact that their basicity is due to the nitrogen atom ·N⁚ has been clearly shown by Pinner and Schwarz (*loc. cit.*) by the formation of a mixture of monoalkylamines by the degradation of alkyl salts of *N*-substituted glyoxalines.

Consideration of the formulæ of the two isomeric dibromodimethylglyoxalines (XI and XII) shows that the basic 3-nitrogen atom:



$$\left.\begin{array}{l}\mathrm{CBr{\cdot}NMe}\\ \|\\ \mathrm{CMe{-\!-}N}\end{array}\right>\mathrm{CBr}$$

(XI.)



$$\left.\begin{array}{l}\mathrm{CMe{\cdot}NMe}\\ \|\\ \mathrm{CBr{-\!-}N}\end{array}\right>\mathrm{CBr},$$

(XII.)

is in both cases in close proximity to the strongly negative substituent bromine atom in the 2-position; the position of the other bromine atom relative to the 3-nitrogen atom is different in the two cases, and it seems reasonable to suppose that 2 : 5-dibromo-1 : 4-dimethylglyoxaline (XI), in which the second bromine atom is at a distance from the 3-nitrogen atom, will be a stronger base than 2 : 4-dibromo-1 : 5-dimethylglyoxaline (XII), in which these groups are close together. On the assumption that this view is correct, the compound melting at 44—45° is 2 : 5-dibromo-1 : 4-dimethylglyoxaline, and consequently the dimethylglyoxaline boiling at 198—199° is 1 : 4-dimethylglyoxaline, the compound melting at 128—129° is 2 : 4-dibromo-1 : 5-dimethylglyoxaline, and the dimethylglyoxaline boiling at 224—225° is 1 : 5-dimethylglyoxaline.

The bearing of these results on the constitution of *iso*pilocarpine has now to be discussed.

By the distillation of this alkaloid with soda-lime, Jowett (Trans., 1903, **83**, 438) obtained a number of glyoxaline derivatives, of which one was shown to be a dimethylglyoxaline. For the purpose of comparison, Jowett and Potter (Trans., 1903, **83**, 464) prepared by the methylation of 4(or 5)-methylglyoxaline an *N*-methyl derivative, which they regarded as a simple substance, either 1 : 4- or 1 : 5-dimethylglyoxaline. The aurichloride and platinichloride of this base, after suitable crystallisation, were shown to be identical with the aurichloride and platinichloride respectively of the dimethylglyoxaline obtained from *iso*pilocarpine; the picrate of the synthetic base, however, although having the same melting point—167°—as the picrate of the dimethylglyoxaline from *iso*pilocarpine, was not identical with the latter, since the mixture melted at 140—145°. These facts led Jowett to the conclusion that the dimethylglyoxalines derived from *iso*pilocarpine, and obtained by the methylation of 4(or 5)-methylglyoxaline respectively, were isomeric and not identical, and he also concluded that they were the 1 : 4- and 1 : 5-dimethylglyoxalines, but that there was no evidence to show which of the two was 1 : 4 and which 1 : 5.

The repetition of the methylation of 4(or 5)-methylglyoxaline on a larger scale, which has been made possible by Windaus and Knoop's discovery (*Ber.*, 1905, **38**, 1166) of a convenient method for the preparation of this compound, has shown that the product obtained is a mixture of the 1 : 4- and 1 : 5-isomerides. A comparison of the properties of the two isomerides and their salts with those of the dimethylglyoxaline from *iso*pilocarpine recorded by Jowett (*loc. cit.*) is tabulated below:

		1 : 4.	1 : 5.	From *iso*-pilocarpine.
Base...............	B. p.	198—199°	224—225°	210—215°
	Sp. gr.................	0·997	1·021	—
	$n_D^{20^\circ}$	1·49042	1·49963	—
Aurichloride	M. p.	137—138°	218—219°	214—215°
	Solubility in alcohol	easily	sparingly	—
Platinichloride ...	M. p.	233°	246°	238—239° *
	Solubility in water.	fairly easily	sparingly	—
Picrate	M. p.	167—168°	168—169°	167°
Hydrochloride ...	M. p.	168—169°	194—195°	—
Hydrogen oxalate.	M. p.	105—106°	133—134°	—

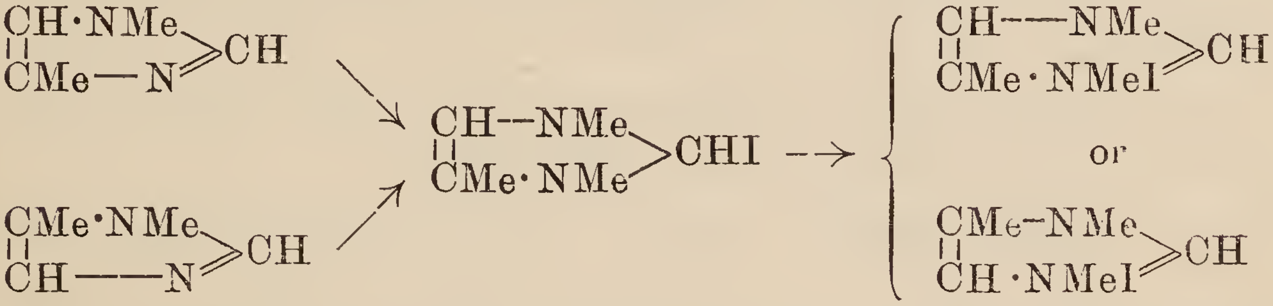
* When heated fairly quickly, this salt melted at 247°.

Through the kindness of Dr. Jowett, the author has had the opportunity of examining specimens of the picrate and platinichloride of the dimethylglyoxaline obtained from *iso*pilocarpine. The picrate melted at 167—168°, and mixtures of approximately equal amounts of this salt with (1) 1 : 4-dimethylglyoxaline picrate at 140—145° and (2) 1 : 5-dimethylglyoxaline picrate at 167—168°. The platinichloride, when slowly heated, decomposed at 238—239°, and mixtures with (1) 1 : 4-dimethylglyoxaline platinichloride at 220° and (2) 1 : 5-dimethylglyoxaline platinichloride at 239°; when fairly quickly heated, however, the platinichloride decomposed at 247°, and the mixture with 1 : 5-dimethylglyoxaline platinichloride at 248°; the platinichloride of the dimethylglyoxaline from *iso*pilocarpine is sparingly soluble in water. Consideration of the table and the above facts shows that the dimethylglyoxaline from *iso*pilocarpine is identical with the isomeride of higher boiling point, which there is good reason to believe is 1 : 5-dimethylglyoxaline.

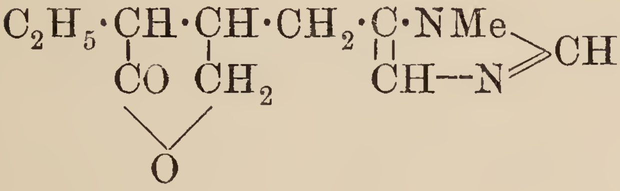
It is evident that Jowett and Potter's synthetic dimethylglyoxaline, which distilled mainly at 203° and had a specific gravity of 1·003, consisted chiefly of the 1 : 4-isomeride of lower boiling point; the picrates of the two isomerides being of a similar solubility in water, they eventually obtained, after crystallisation of their picrate, the pure picrate of 1 : 4-dimethylglyoxaline; recrystallisation of the aurichloride of their base from alcohol, however, gave them the pure 1 : 5-dimethylglyoxaline aurichloride, which is sparingly soluble in this solvent, whereas 1 : 4-dimethylglyoxaline aurichloride is easily soluble; similarly, recrystallisation of the platinichloride of their base from water yielded 1 : 5-dimethylglyoxaline platinichloride, which is sparingly soluble in water, the

1 : 4-dimethylglyoxaline platinichloride remaining in the mother liquors.

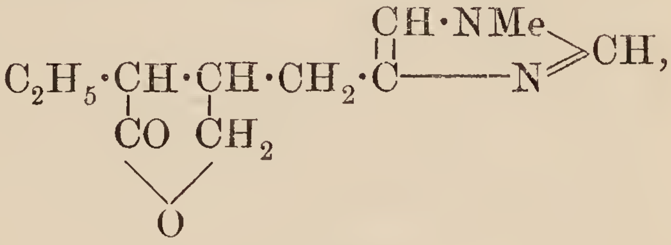
The methiodide prepared by Jowett and Potter from the synthetic dimethylglyoxaline may be obtained by the action of methyl iodide on either 1 : 4- or 1 : 5-dimethylglyoxaline. A similar case of the formation of only one methiodide from two isomeric benziminazoles has previously been described and explained by Otto Fischer (*loc. cit.*), on the assumption that methyl iodide is combined at the unsaturated linking, and that the compound produced then rearranges itself, forming the more stable of the two possible substituted ammonium iodides. This explanation is also applicable to the present case, and may be represented graphically as follows:



In conclusion, it may be pointed out that of the two alternative isomeric formulæ (I) and (II) put forward by Jowett (*loc. cit.*) for *iso*pilocarpine (compare also Pinner and Schwarz, *loc. cit.*), (I), which depicts the alkaloid as a 1 : 5-substituted glyoxaline, is supported by the fresh evidence now brought forward:



(I.)



(II.)

and since Jowett has shown (Trans., 1905, **87**, 794) that *iso*pilocarpine and pilocarpine are stereoisomerides, this evidence is equally applicable to the latter alkaloid.

EXPERIMENTAL.

Methylation of 4(*or* 5)-*Methylglyoxaline: Separation of the Isomeric* 1 : 4- *and* 1 : 5-*Dimethylglyoxalines.*

One hundred grams of 4(or 5)-methylglyoxaline were well shaken with 360 c.c. of 20 per cent. aqueous sodium hydroxide and 25 grams of methyl sulphate, the mixture being kept cold by running water; five further quantities of 120 c.c. of 20 per cent. aqueous sodium hydroxide and 25 grams of methyl sulphate were added successively with thorough shaking during the course of an hour. The liquor was then completely extracted with chloroform, and the extract dried with anhydrous potassium carbonate. After removal of the solvent, the resulting oil was distilled once under diminished pressure, and then fractionated three times under normal pressure, fractions being collected every 10° between 190° and 250°. As a considerable proportion of the oil distilled above 250°, it appeared that a part of the 4(or 5)-methylglyoxaline had escaped methylation, and the fractions boiling above 230°, and amounting to 31 grams, were consequently re-methylated. The product was fractionated, and the fractions suitably combined with those from the first methylation.

At this stage the products were as follows:

B. p...	190—200°	200—205°	205—210°	210—215°	215—220°	220—230°
Grams	6·0	10·0	16·2	7·5	8·0	5·0

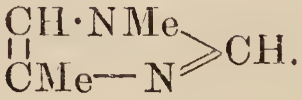
After twelve fractional distillations of the above under normal pressure, the following fractions were obtained:

B. p...	195—200°	200—202°	202—205°	205—210°	210—215°	215—220°	220—225°	above 225°.
Grams	17·0	5·0	3·8	3·6	2·3	4·5	8·4	3·8

The first fraction, b. p. 195—200°, distilled mainly at 198—199°, and represented nearly pure 1 : 4-dimethylglyoxaline. It was neutralised with dilute hydrochloric acid, and precipitated with picric acid, when 42 grams of the picrate, having the correct melting point, 167—168° (corr.), were obtained. After regeneration from the picrate, 1 : 4-dimethylglyoxaline distilled at 198—199° (corr.).

The fraction distilling at 220—225° was similarly converted into the picrate, and gave at first a quantity of pure 1 : 5-dimethylglyoxaline picrate, melting at 168—169° (corr.); the mother liquors and the picrates from adjacent fractions gave the same salt in a crude condition, and this was purified by crystallisation from water; altogether 19 grams of this salt were obtained in a pure state. After regeneration from the picrate, 1 : 5-dimethylglyoxaline distilled at 224—225° (corr.).

1 : 4-*Dimethylglyoxaline*,



$$\left.\begin{array}{l}\mathrm{CH{\cdot}NMe}\\ \Vert\\ \mathrm{CMe{-}N}\end{array}\right>\mathrm{CH}.$$

The base is a colourless, mobile, deliquescent liquid, having an odour somewhat similar to that of pyridine. It boils at 198—199° (corr.), and did not solidify after keeping for several hours in an ice-chest. It is miscible with water, alcohol, ether, and chloroform in all proportions, and a considerable amount of heat is developed when it is mixed with water or chloroform. It has a sp. gr. of 0·997 at 15·5°/15·5°, and a refractive index of 1·49042 at 20°:

0·1495 gave 0·3419 CO_2 and 0·1121 H_2O. C = 62·4; H = 8·3.
0·0538 „ 13·7 c.c. N_2 at 25° and 774 mm. N = 29·0.
$C_5H_8N_2$ requires C = 62·5; H = 8·4; N = 29·2 per cent.

The *hydrochloride* was obtained by neutralising the base with absolute alcoholic hydrochloric acid, and evaporating the salt to dryness in a vacuum desiccator over sulphuric acid. It separated in long, colourless, very deliquescent needles, which melted at 168—169° (corr.):

0·1408 gave 0·1537 AgCl. Cl = 27·0.
$C_5H_8N_2,HCl$ requires Cl = 26·7 per cent.

The *hydrogen oxalate* crystallises from absolute alcohol in prismatic needles, which, after drying in a vacuum, melt at 105—106° (corr.). This salt is readily soluble in water, but sparingly so in absolute alcohol:

0·1600, dried in a vacuum, gave 0·2637 CO_2 and 0·0841 H_2O. C = 44·9; H = 5·9.
$C_5H_8N_2,C_2H_2O_4$ requires C = 45·1; H = 5·4 per cent.

The *aurichloride* crystallises from alcohol in yellow, transparent, pointed prisms, which melt at 137—138° (corr.). It is sparingly soluble in water, readily so in cold alcohol, and very readily so in hot alcohol:

0·1725 gave 0·0869 CO_2 and 0·0371 H_2O. C = 13·7; H = 2·4.
0·2224 „ 0·1010 Au. Au = 45·4.
$C_5H_8N_2,HAuCl_4$ requires C = 13·8; H = 2·1; Au = 45·2 per cent.

The *platinichloride* crystallises from water in long, orange splinters, which decompose at 233° (corr.). It is fairly readily soluble in cold water, readily so in hot water, but almost insoluble in alcohol:

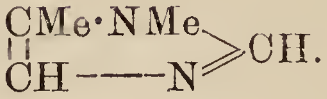
0·2015 gave 0·0647 Pt. Pt = 32·1.
$(C_5H_8N_2)_2,H_2PtCl_6$ requires Pt = 32·4 per cent.

The picrate and methiodide have already been described by Jowett and Potter (*loc. cit.*), who obtained them from the synthetic dimethylglyoxaline.

The picrate crystallises from water in beautiful, long, flat, yellow needles, which melt at 167—168° (corr.). It is sparingly soluble in cold water, but readily so in hot water.

The methiodide is produced with considerable evolution of heat when equimolecular proportions of the base and methyl iodide are mixed. It crystallises from absolute alcohol in long, stout, colourless splinters, which, when dried at 100°, melt to a viscous liquid at 160—163° (corr.). When the salt is mixed with an equal amount of the methiodide of 1:5-dimethylglyoxaline, its melting point is unchanged.

1 : 5-*Dimethylglyoxaline*,



$$\left.\begin{matrix}\mathrm{CMe{\cdot}NMe} \\ \| \\ \mathrm{CH{-}{-}{-}{-}N}\end{matrix}\right>\mathrm{CH}.$$

The base is a colourless, mobile, deliquescent liquid, having an odour somewhat similar to that of pyridine, but less intense than that of the 1 : 4-isomeride. It boils at 224—225° (corr.), and did not solidify after being kept for several hours in an ice-chest. It is miscible with water, alcohol, ether, and chloroform in all proportions, and a considerable amount of heat is developed when it is mixed with water or chloroform. It has a sp. gr. of 1·021 at 15·5°/15·5°, and a refractive index of 1·49963 at 20°:

0·1516 gave 0·3451 CO_2 and 0·1165 H_2O. C = 62·1; H = 8·6.
0·0743 „ 18·8 c.c. N_2 at 24° and 770 mm. N = 28·8.
$C_5H_8N_2$ requires C = 62·5; H = 8·4; N = 29·2 per cent.

The *hydrochloride*, prepared from the base and absolute alcoholic hydrochloric acid, separates in rectangular, oblong plates, melting at 194—195° (corr.), on evaporation of the solution in a vacuum over sulphuric acid. This salt is very deliquescent:

0·2134 gave 0·2313 AgCl. Cl = 26·8.
$C_5H_8N_2,HCl$ requires Cl = 26·7 per cent.

The *hydrogen oxalate* crystallised from absolute alcohol in stout, prismatic needles, which sintered at 132° and melted at 133—134° (corr.). This salt is readily soluble in water, but sparingly so in absolute alcohol:

0·1515 gave 0·2523 CO_2 and 0·0764 H_2O. C = 45·4; H = 5·7.
$C_5H_8N_2,C_2H_2O_4$ requires C = 45·1; H = 5·4 per cent.

The aurichloride, platinichloride, and picrate of this base have previously been prepared by Jowett (Trans., 1903, **87**, 445) from the dimethylglyoxaline obtained by the distillation of *iso*pilocarpine with soda-lime; the aurichloride and platinichloride were also prepared from synthetic dimethylglyoxaline (Jowett and Potter, *loc. cit.*), and identified with the corresponding salts obtained from the alkaloid. It is therefore only necessary to describe them shortly.

The aurichloride crystallised from alcohol in yellow needles, which sintered and deepened in colour at 165° and decomposed at 218—219° (corr.). This salt is sparingly soluble in water or alcohol.

The platinichloride separated on adding platinic chloride to the aqueous solution of the hydrochloride in orange, rectangular leaflets, which began to darken at 239° and decomposed at 246° (corr.). When heated more rapidly, this salt decomposes at 249° (corr.). This salt is sparingly soluble in cold water, and almost insoluble in alcohol.

The picrate crystallised from water in short, yellow needles, which melted at 168—169° (corr.). It is sparingly soluble in cold water, but readily so in hot.

A mixture of approximately equal parts of this salt and of 1 : 4-dimethylglyoxaline picrate gradually sintered, softened considerably at 135°, and melted to a clear liquid at 140—145°.

The methiodide is formed with considerable evolution of heat when equimolecular proportions of 1 : 5-dimethylglyoxaline and methyl iodide are mixed, and, after crystallisation from absolute alcohol, forms long, stout, colourless splinters, which, when dried at 100°, melt at 160—163° (corr.); this salt is identical with 1 : 4-dimethylglyoxaline methiodide (p. 1822).

Bromination of 4(*or* 5)-*Methylglyoxaline.*

To a solution of 100 grams of 4(or 5)-methylglyoxaline in 600 c.c. of chloroform, 200 grams of bromine diluted to 300 c.c. with chloroform were added drop by drop with mechanical stirring, the temperature being maintained at $-10°$ to $-12°$. The addition of the bromine occupied an hour, and the liquor was stirred for another half hour. It then formed a clear, pale brown solution, but when removed from the freezing mixture became turbid and began to separate into two layers, the upper one of chloroform, and the lower of brown oil, which soon began to crystallise. After keeping for a few hours, the crystals were separated from oil and chloroform by filtration, and washed with chloroform. The oil and chloroform were then separated, and the chloroform distilled, when a small further quantity of oil remained, which was added to the separated oil.

The crystals were heated for half an hour on the water-bath with a litre of water, when a part remained undissolved, and after keeping overnight, 27 grams of dibromo-4(or 5)-methylglyoxaline, melting at 210°, were collected (mother liquor M).

The oil was also heated for half an hour on the water-bath with a litre of water, but no crystals separated on keeping the solution; this was combined with the mother liquor M and fractionally precipitated with ammonia, when successively small fractions, melting at 205°, 175°, and 120—135°, and 30 grams melting at 145°, were obtained. On evaporating the ammoniacal liquor to low bulk, a further quantity of 35 grams of crystals, melting at 145°, separated; 33 grams of brown oil, which became partly crystalline, were obtained by extracting the mother liquor with chloroform, and a further 9 grams of brown oil were similarly extracted after the addition of aqueous sodium carbonate.

The various products were worked up as follows. The fractions which melted above 200° gave, on recrystallisation from ethyl acetate, pure dibromo-4(or 5)-methylglyoxaline, m. p. 215—216° (corr.); those melting at 145°, after recrystallisation from the same solvent, gave pure bromo-4(or 5)-methylglyoxaline, m. p. 154—155° (corr.). The mother liquors, after the removal of ethyl acetate and also those precipitated fractions which were obviously mixtures, were again separated by fractional dissolution in dilute hydrochloric acid and fractional precipitation with ammonia; in this way a further partial separation into crude dibromo-derivative melting at about 205—210°, crude bromo-derivative melting at about 135—145°, and intermediate fractions, was effected. On crystallisation of these fractions from ethyl acetate, further quantities of the pure compounds were obtained, and the residues were again subjected to the same cycle of operations.

The oil extracted by chloroform from the ammoniacal solution was extracted with water, which removed a quantity of 4(or 5)-methylglyoxaline, and, after fractional treatment with acid and alkali, gave further small quantities of the di- and mono-bromo-derivatives; the 9 grams of brown oil extracted by chloroform after the addition of sodium carbonate were nearly pure 4(or 5)-methylglyoxaline, and crystallised on keeping.

The total yield amounted to 36 grams of pure dibromo-4(or 5)-methylglyoxaline and 67 grams of pure bromo-4(or 5)-methylglyoxaline; there were also obtained 25 grams of viscid, dark brown, partly crystalline oil, which was not further purified, and about 18 grams of nearly pure unchanged 4(or 5)-methylglyoxaline.

The bromination has been carried out at various temperatures with the view of determining the best conditions for the production of the mono-bromo-derivative, with the following result:

One hundred grams of 4(or 5)-methylglyoxaline brominated at

5 to 10°	gave	52	grams of	dibromo- and	58	grams of	monobromo-	derivative
−4 to −7°	,,	46	,,	,,	62	,,	,,	,,
−10 to −12°	,,	36	,,	,,	67	,,	,,	,,

These figures refer, of course, to the quantities of pure compounds isolated; in each case there was also a dark brown, sticky residue, which could not readily be further purified, and some unchanged 4(or 5)-methylglyoxaline.

It should be mentioned here that when the bromination is carried out at 5° to 10° or −4° to −7°, the chloroform solution does not remain clear throughout, but gradually becomes turbid, and eventually crystals separate during the addition of bromine.

Bromo-4(*or* 5)-*methylglyoxaline* (VIII, VIIIa, IX or IXa, p. 1816).

This base crystallises from ethyl acetate in long, glistening, silky needles, which melt at 154—155° (corr.). It is sparingly soluble in cold water, fairly readily so in boiling water, and readily so in alcohol or ethyl acetate. It is soluble in dilute acids, dilute aqueous sodium hydroxide, or in a large excess of 10 per cent. aqueous ammonia, but not in 10 per cent. aqueous sodium carbonate:

0·1503 gave 0·1655 CO_2 and 0·0443 H_2O. $C=30·0$; $H=3·3$.
0·1004 „ 14·7 c.c. N_2 at 16° and 768 mm. $N=17·3$.
0·1537 „ 0·1809 AgBr. $Br=50·1$.
$C_4H_5N_2Br$ requires $C=29·8$; $H=3·1$; $N=17·4$; $Br=49·6$ per cent.

Aqueous solutions of this compound give with silver nitrate solution a white precipitate of the *silver* salt, which crystallises from boiling water in colourless, silky needles.

A solution of this base in dilute aqueous sodium hydroxide becomes deep orange in colour on the addition of aqueous sodium diazobenzene-*p*-sulphonate.

The *hydrogen oxalate* crystallises from water in colourless, prismatic needles, which begin to sinter at 205°, and decompose at 210° (corr.). It is anhydrous, and is very readily soluble in boiling water, but only moderately so in cold water:

0·1532 gave 0·1628 CO_2 and 0·0404 H_2O. $C=29·0$; $H=3·0$.
$C_4H_5N_2Br,C_2H_2O_4$ requires $C=28·7$; $H=2·8$ per cent.

Dibromo-4(*or* 5)-*methylglyoxaline* (X or Xa, p. 1816).

This compound crystallises from ethyl acetate in glistening, prismatic rods, which melt at 215—216° (corr.). It is almost insoluble in cold water, sparingly soluble in hot water, readily soluble in alcohol, and somewhat sparingly so in ethyl acetate. It is soluble in excess of dilute acids, and readily soluble in aqueous sodium hydroxide or 10 per cent. aqueous ammonia, but not in 10 per cent. aqueous sodium carbonate:

0·1489 gave 0·1111 CO_2 and 0·0261 H_2O. $C=20·3$; $H=2·0$.
0·1516 „ 15·8 c.c. N_2 at 21° and 764 mm. $N=11·9$.
0·1490 „ 0·2351 AgBr. $Br=67·1$.
$C_4H_4N_2Br_2$ requires $C=20·0$; $H=1·7$; $N=11·7$; $Br=66·7$ per cent.

Aqueous solutions of this compound give with silver nitrate solution a white precipitate of the *silver* salt.

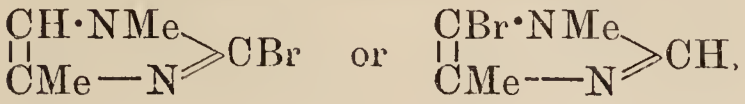
A solution of this base in dilute aqueous sodium hydroxide becomes deep orange in colour on the addition of aqueous sodium diazobenzene-*p*-sulphonate.

Methylation of Bromo-4(or 5)-methylglyoxaline.

Seventy grams of bromo-4(or 5)-methylglyoxaline were suspended in 300 c.c. of 10 per cent. aqueous sodium hydroxide, and well shaken while kept cold in running water with 14 grams of methyl sulphate, yielding a nearly clear solution. Quantities of 100 c.c. of 10 per cent. aqueous sodium hydroxide and 14 grams of methyl sulphate were added four times more, so that the total amounts used for the methylation were 700 c.c. of 10 per cent. aqueous sodium hydroxide and 70 grams of methyl sulphate. The addition of these quantities was carried through in one hour, and the mixture well shaken for ten minutes after the last addition.

The oil which had separated was then collected, and the aqueous liquor completely extracted with chloroform; the oil and chloroform were then mixed, dried with anhydrous potassium carbonate, and the solvent distilled. The chloroform residue amounted to 66 grams of brown oil, representing the mixed isomeric *N*-methyl derivatives. The mother liquor gave no more oil on re-methylation. The oil (66 grams) was combined with a similar product (44 grams) obtained by the methylation of another 50 grams of bromo-4(or 5)-methylglyoxaline, and kept overnight in a vacuum desiccator, when a quantity of 2(or 4)-bromo-1:5-dimethylglyoxaline separated in large, flat needles; this was collected, and amounted to 25 grams. The crystals and the oily liquor from which they separated were separately converted into the hydrogen oxalates, and crystallised from water; from the former a quantity of 2(or 4)-bromo-1:5-dimethylglyoxaline hydrogen oxalate was readily obtained in pure condition (m. p. 146—147°); from the latter, however, various crops of mixed hydrogen oxalates of the two isomerides, melting between about 85° and 95°, were obtained, and these were subjected to a prolonged fractional crystallisation from water. It was found that, on crystallising a mixture melting at about 90° from rather less than its own weight of water, fairly pure 2(or 5)-bromo-1:4-dimethylglyoxaline hydrogen oxalate, melting at 93—95°, would separate in large crystals on keeping overnight, and that the mother liquor, on scratching, would deposit a certain amount of crude 2(or 4)-bromo-1:5-dimethylglyoxaline hydrogen oxalate as a crystalline powder, melting at about 140°. Eventually, there were obtained altogether (from 110 grams of the mixed isomerides) 84 grams of pure 2(or 5)-bromo-1:4-dimethylglyoxaline hydrogen oxalate, melting at 95—97°, and 12 grams of the same salt in a fairly pure state, also 55 grams of pure 2(or 4)-bromo-1:5-dimethylglyoxaline hydrogen oxalate, melting at 146—147°, and 8 grams of the same salt in a moderately pure state, together with 10 grams of residues.

2(*or* 5)-*Bromo*-1 : 4-*dimethylglyoxaline*,



$$\left.\begin{matrix}CH\cdot NMe\\ \|\\ CMe-N\end{matrix}\right>CBr \quad \text{or} \quad \left.\begin{matrix}CBr\cdot NMe\\ \|\\ CMe-N\end{matrix}\right>CH.$$

This base was obtained, after regeneration from the pure hydrogen oxalate and extraction with ether, as an oil, which gradually solidified. It crystallises from anhydrous ether in beautiful, clear, colourless, quadrilateral plates, which melt at 40—45° (corr.), after sintering from about 35°.

The base is very deliquescent, readily taking up water, and forming an oil which is sparingly soluble in water. It is not more soluble in alkalis than in water, but is readily soluble in dilute acids. It is readily soluble in alcohol, ether, or chloroform:

0·2076 gave 0·2636 CO_2 and 0·0725 H_2O. C = 34·6; H = 3·9.
0·1769 „ 0·1908 AgBr. Br = 45·9.
$C_5H_7N_2Br$ requires C = 34·3; H = 4·0; Br = 45·7 per cent.

The *hydrochloride* crystallises from water in clear prisms, which, after drying at 100°, melt at 196—197° (corr.). It is very readily soluble in water or alcohol, but very sparingly so in acetone. Its aqueous solution reacts strongly acid:

0·1633 * gave 0·1681 CO_2 and 0·0567 H_2O. C = 28·1; H = 3·9.
0·2314 * „ 0·1583 AgCl. Cl = 16·9.
$C_5H_7N_2Br,HCl$ requires C = 28·4; H = 3·8; Cl = 16·8 per cent.

The *hydrogen oxalate* crystallises from water in large, irregular prisms, which melt at 95—97° (corr.), and contain one molecule of water of crystallisation. After drying, first in a vacuum and then at 100°, it melts at 133—135° (corr.). This salt is very readily soluble in hot water, and soluble in less than two and a-half times its weight of water at 25°:

0·1516 † gave 0·1659 CO_2 and 0·0533 H_2O. C = 29·8; H = 3·9.
0·1611 † „ 13·5 c.c. N_2 at 20° and 760 mm. N = 9·6.
0·2093 † lost 0·0137 at 100°. H_2O = 6·5.
$C_5H_7N_2Br,C_2H_2O_4,H_2O$ requires C = 29·7; H = 3·9; N = 9·9; H_2O = 6·4 per cent.

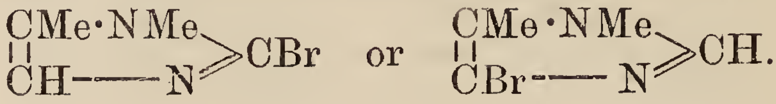
0·1440 * gave 0·1688 CO_2 and 0·0457 H_2O. C = 32·0; H = 3·6.
0·1834 * „ 0·1293 AgBr. Br = 30·0.
$C_5H_7N_2Br,C_2H_2O_4$ requires C = 31·7; H = 3·4; Br = 30·2 per cent.

The *picrate* crystallises from boiling water in long, flat, yellow needles, which melt at 223—224° (corr.), after sintering earlier. It is very sparingly soluble in water:

0·1534 gave 0·1835 CO_2 and 0·0362 H_2O. C = 32·6; H = 2·6.
$C_5H_7N_2Br,C_6H_3O_7N_3$ requires C = 32·7; H = 2·5 per cent.

* Dried at 100°. † Air-dried salt.

2(*or* 4)-*Bromo*-1 : 5-*dimethylglyoxaline*,



This base crystallises from ether in colourless, transparent splinters (or plates), which melt at 77—78° (corr.). When moistened with water, it becomes oily, and on the addition of a large quantity passes into solution. It is not more soluble in alkalis than in water, but dissolves readily in dilute acids. It is readily soluble in the usual organic solvents, with the exception of light petroleum:

0·1551 gave 0·1941 CO_2 and 0·0596 H_2O. C = 34·1; H = 4·3.
0·1517 „ 0·1917 CO_2 „ 0·0584 H_2O. C = 34·5; H = 4·3.
0·1683 „ 22·3 c.c. N_2 at 13° and 770 mm. N = 15·9.
0·1493 „ 0·1615 AgBr. Br = 46·0.
$C_5H_7N_2Br$ requires C = 34·3; H = 4·0; N = 16·0; Br = 45·7 per cent.

The *hydrochloride* crystallises from moist acetone in rectangular leaflets, which contain about half a molecular proportion of water of crystallisation, and melt at 93—94° (corr.). After drying at 100°, this salt melts at 172—174° (corr.). It is very readily soluble in water or alcohol, but sparingly so in acetone. Its aqueous solution reacts strongly acid:

0·2020 † lost 0·0106 in a vacuum over H_2SO_4. H_2O = 5·2.
$C_5H_7N_2Br,HCl,\frac{1}{2}H_2O$ requires H_2O = 4·1 per cent.

0·1569 * gave 0·1614 CO_2 and 0·0582 H_2O. C = 28·1; H = 4·2.
0·1912 * „ 0·1296 AgCl. Cl = 16·8 per cent.
$C_5H_7N_2Br,HCl$ requires C = 28·4; H = 3·8; Cl = 16·8 per cent.

The *hydrogen oxalate* crystallises from water in magnificent, diamond-shaped, transparent plates, which melt at 146—147° (corr). This salt is anhydrous. It is very readily soluble in hot water, and soluble in four times its weight of cold water:

0·1489 gave 0·1743 CO_2 and 0·0494 H_2O. C = 31·9; H = 3·7.
0·1808 „ 16·0 c.c. N_2 at 20° and 767 mm. N = 10·2.
$C_5H_7N_2Br,C_2H_2O_4$ requires C = 31·7; H = 3·4; N = 10·6 per cent.

The *picrate* crystallises from water in long, yellow needles, which melt at 198—199° (corr.), after sintering earlier. It is very sparingly soluble in water:

0·1518 gave 0·1830 CO_2 and 0·0346 H_2O. C = 32·9; H = 2·6.
$C_5H_7N_2Br,C_6H_3O_7N_3$ requires C = 32·7; H = 2·5 per cent.

* Dried at 100°. † Air-dried salt.

Methylation of Dibromo-4(or 5)-methylglyoxaline.

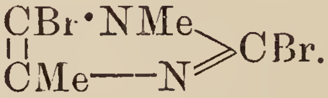
Fifty-five grams of dibromo-4(or 5)-methylglyoxaline were dissolved in 140 c.c. of 10 per cent. aqueous sodium hydroxide, and well shaken with 15 grams of methyl sulphate (half the calculated quantity), added in small quantities with thorough stirring and cooling under the tap. The solution began to deposit crystals shortly after the first addition of methyl sulphate; these were collected at the end of the methylation, and amounted to 24 grams. The mother liquor, after re-methylation with 90 c.c. of 10 per cent. aqueous sodium hydroxide and 15 grams of methyl sulphate, afforded another 20 grams of crystals, and the final mother liquor, when again methylated with the same quantities, gave a further 8 grams. The total yield of the mixed isomerides was therefore 52 grams, and each crop behaved in the same way on heating, sintering at 75°, and melting at 90—100. The mixture was separated by distillation with steam, when 2 : 5-dibromo-1 : 4-dimethylglyoxaline passed over very readily, and separated as a colourless oil, which solidified on cooling, and melted at 44—45°. As the distillation proceeded, a small quantity of colourless needles also separated in the receiver, and contaminated the oil, raising the melting point of the solidified oil somewhat; on redistilling with steam, however, the pure low melting isomeride again passed over first. The aqueous distillates still contain a considerable amount of this substance, but the bulk of it may be recovered by distilling these liquors, when it passes over quickly and largely separates from the first fraction; the remainder may be recovered by extraction with ether. The yield of 2 : 5-dibromo-1 : 4-dimethylglyoxaline amounted to 20·2 grams.

The residue of the steam distillation, consisting of 2 : 4-dibromo-1 : 5-dimethylglyoxaline, was purified by crystallisation from ethyl acetate, when it was obtained in beautiful, long, flat needles, which melted at 128—129° (corr.), and in quantity amounting to 20·1 grams.

The separation of the two isomerides may also be effected by crystallisation of the mixture from ethyl acetate; thus, 41 grams of the mixture (m. p. 90—100°), crystallised from 80 c.c. of ethyl acetate, gave at once 9·7 grams, melting at 125°, and, on concentrating, in various crops, 10·9 grams melting between 115° and 123°, then 1·5 grams melting at 90—100°; after removing the solvent from the mother liquor, an oil was obtained; this became solid, melted at 40—46°, and amounted to 17 grams.

By crystallisation of the fractions of high melting point from ethyl acetate, 18 grams of pure 2 : 4-dibromo-1 : 5-dimethylglyoxaline, and by distillation of the fractions of low melting point with steam, 13 grams of pure 2: 5-dibromo-1: 4-dimethylglyoxaline were obtained.

2 : 5-*Dibromo*-1 : 4-*dimethylglyoxaline*,



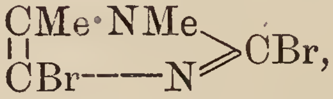
$\left.\begin{array}{l}\mathrm{CBr{\cdot}NMe}\\ \|\\ \mathrm{CMe{-}{-}N}\end{array}\right\rangle\mathrm{CBr}.$

This compound crystallises from light petroleum in flat, prismatic rods, which sinter from 42° and melt at 44—45° (corr.).

It is very easily volatile with steam, sparingly soluble in water, and very readily soluble in the usual organic solvents. It is soluble in dilute acids, but not in alkalis:

0·1516 gave 0·1325 CO_2 and 0·0322 H_2O. C = 23·9; H = 2·4.
0·1546 ,, 14·3 c.c. N_2 at 16° and 763 mm. N = 10·8.
0·1034 ,, 0·1538 AgBr. Br = 63·3.
$C_5H_6N_2Br_2$ requires C = 23·6; H = 2·4; N = 11·0; Br = 63·0 per cent.

2 : 4 - Dibromo - 1 : 5 - dimethylglyoxaline,



$\left.\begin{array}{l}\mathrm{CMe{\cdot}NMe}\\ \|\\ \mathrm{CBr{-}{-}N}\end{array}\right\rangle\mathrm{CBr},$

has previously been described by Jowett and Potter (*loc. cit.*). It melts at 128—129° (corr.), and is soluble in 10 per cent. hydrochloric acid; it is only slightly volatile with steam.

The relative affinity of the two isomeric dibromodimethylglyoxalines has been roughly determined as follows.

0·5 Gram of each isomeride was separately dissolved in 10 c.c. of 10 per cent. aqueous hydrochloric acid, and each solution well shaken with 25 c.c. of chloroform. The chloroform extracts were filtered through a dry filter and evaporated to dryness. In the case of 2: 5-dibromo-1: 4-dimethylglyoxaline, the chloroform residue amounted to 0·05 gram, melting at 44—45° (corr.), that is, 10 per cent. of the quantity of base present; whilst in the case of 2: 4-dibromo-1: 5-dimethylglyoxaline, the chloroform residue amounted to 0·31 gram, melting at 128—129° (corr.), that is, 62 per cent. of the quantity of base present.

Bromination of 1: 4-*Dimethylglyoxaline.*

Three grams of 1: 4-dimethylglyoxaline were dissolved in 6 c.c. of chloroform, cooled with ice, and treated with a solution of 5 grams of bromine made up to 5 c.c. with chloroform added drop by drop in ten minutes with thorough stirring. On keeping, the red liquor remained clear; it was shaken with ammonia and water, dried with anhydrous potassium carbonate, and the solvent removed.

The residual oil was dissolved in just sufficient 10 per cent. aqueous hydrochloric acid, diluted, and distilled with steam; the first 30 c.c. of distillate carried over 0·1 gram of 2: 5-dibromo-1: 4-dimethylglyoxaline as an oil which solidified on keeping, and melted at 42—44°; a further 70 c.c. of clear distillate were collected, mixed with the 30 c.c. of distillate from which the solid had been separated, and redistilled, when a further 0·09 gram of the same dibromo-compound was obtained.

The acid liquor was then rendered alkaline, and again distilled with steam; the distillate, however, was quite bright even at the commencement, indicating that no considerable amount of the dibromo-compound was contained in the liquor. The liquor was then completely extracted with chloroform, giving 2·7 grams of brown oil; this was converted into the hydrogen oxalate and crystallised from water, when 3·0 grams of 2(or 5)-bromo-1 : 4-dimethylglyoxaline hydrogen oxalate, melting at 93—94°, separated; after recrystallisation from water, this salt melted at 95—97° (corr.).

Bromination of 1 : 5-*Dimethylglyoxaline.*

Three grams of 1 : 5-dimethylglyoxaline were brominated with 5 grams of bromine under the same conditions as its isomeride. The resulting orange-red liquor in this case deposited crystals on keeping, but these were not separated, the mixture being extracted several times with water to remove easily soluble hydrobromides.

The chloroform solution was then shaken with dilute ammonia, dried, and distilled, when 2·8 grams of 2 : 4-dibromo-1 : 5-dimethylglyoxaline were obtained as a buff, crystalline residue, melting at 127°; after recrystallisation from ethyl acetate, this compound melted at 128—129° (corr.).

The base regenerated from the aqueous extract of the chloroform solution amounted to 1·2 grams, and formed a pale brown oil; this was converted into the hydrogen oxalate, and twice recrystallised from water, when 0·3 grams of 2(or 4)-bromo-1 : 5-dimethylglyoxaline hydrogen oxalate, melting at 146—147° (corr.), were obtained.

The author wishes to take this opportunity of thanking Dr. Jowett, not only for his introduction to this subject, but also for his kind advice and interest throughout the investigation.

THE WELLCOME CHEMICAL WORKS,
DARTFORD, KENT.

R. CLAY AND SONS, LTD., BREAD ST. HILL, E.C., AND BUNGAY, SUFFOLK.

2

XLIII.—*Experiments on the Formation of 4(or 5)-β-Aminoethylglyoxaline from Histidine.*

By Arthur James Ewins and Frank Lee Pyman.

4(or 5)-β-Aminoethylglyoxaline, the base derived from the naturally occurring amino-acid histidine (α-amino-β-glyoxaline-4(or 5)-propionic acid) by the removal of carbon dioxide from the latter has recently become of considerable interest and importance on account of its occurrence in extracts of ergot (Barger and Dale, Trans., 1910, **97**, 2592) and very great physiological activity (Dale and Laidlaw, *J. Physiol.*, 1910, **41**, 318). It has hitherto been obtained by two methods: (1) by synthesis; (2) by the action of putrefactive organisms on histidine itself.

The base was first synthesised by Windaus and Vogt (*Ber.*, 1907, **40**, 3691) from β-glyoxaline-4(or 5)-propionic acid by Curtius's method. More recently, Ackermann (*Zeitsch. physiol. Chem.*, 1910, **65**, 504) has succeeded in obtaining a relatively large yield of the base by the putrefaction of histidine.

Neither method is very satisfactory, since the first is somewhat complex and expensive, while the yields are by no means good. The second method is wholly uncertain in its results. The object of our investigation was therefore to endeavour to find a simple method of obtaining the base directly from histidine, which is comparatively easily obtainable. In this we were only partly successful, since we were able to obtain only moderate yields of the base by the action of acids in sealed tubes at a temperature of from 265° to 270°. This last factor (temperature) made it a matter of very great difficulty to obtain anything like large amounts of the base. The results obtained, however, were deemed of sufficient interest to form the subject of the present communication.

Experiments were first carried out to determine whether, as in the case of the formation of *p*-hydroxyphenylethylamine from tyrosine, carbon dioxide could be removed from histidine by direct heating. It was found, however, that under varying conditions only a very small amount (0·3 to 1·0 per cent.) of base could be obtained, and the method was abandoned.

By directly heating the monobenzoyl derivative of histidine and subsequently hydrolysing, a somewhat better yield (10 to 20 per cent.) of the base was obtained.

The effect of various acids under varying conditions of temperature and concentration was then investigated, and it was found that yields of base amounting to about 25 per cent. of the theoretical could be obtained with concentrated hydrochloric acid, moderately dilute sulphuric acid, and fused potassium hydrogen sulphate under suitable conditions. After heating for three hours with acids at temperatures below 240°, no formation of 4(or 5)-β-aminoethylglyoxaline took place. At about 240° very little of the base was obtained, the main product of the reaction being *r*-histidine, which had previously been prepared by Fränkel (*Beitr. Chem. Physiol. Path.*, 1906, **8**, 156) in a similar manner. As the temperature was raised, the yield of base gradually improved, and reached a maximum (about 25 per cent. of the theoretical) at about 265—270°. Further increase of temperature led to diminished yield of 4(or 5)-β-aminoethylglyoxaline. With phosphoric acid (44 per cent.) at 250°, no base was produced, nor did the use of hydrogen bromide in acetic acid solution at somewhat lower temperatures yield any better results.

The progress of the work was very greatly facilitated by the physiological estimation of the yield of base in many of our experiments. This was kindly undertaken for us by Dr. H. H. Dale and Dr. P. P. Laidlaw, to whom we wish to express our indebtedness and thanks.

During the course of the investigation some hitherto undescribed salts of histidine and 4(or 5)-β-aminoethylglyoxaline were prepared, and are now described.

EXPERIMENTAL.

The Action of Concentrated Hydrochloric Acid on Histidine.

One gram of histidine hydrochloride was heated in a sealed tube with 2 c.c. of concentrated hydrochloric acid to 270° for three hours. The solution was concentrated and neutralised. To the boiling solution was added an excess of solid picric acid. On cooling, a crystalline precipitate separated, which was collected and freed from picric acid by extraction with ether. The residue, when recrystallised from water, gave 0·2 gram of 4(or 5)-β-aminoethylglyoxaline dipicrate, melting at 233—235°.

The Action of Dilute Sulphuric Acid.

(*a*) *At* 265—270°.—Two grams of histidine monohydrochloride were heated in a sealed tube to 265—270° for three hours with 4 c.c. of a 20 per cent. aqueous solution of sulphuric acid. The reaction product (a dark brown liquid) was treated with sodium carbonate solution until no further precipitate separated, filtered, and the filtrate neutralised and concentrated to about 15 c.c. An equal volume of cold saturated aqueous solution of picric acid was added, and the amorphous precipitate quickly collected. To the filtrate was added 1·5 grams of picric acid in hot saturated aqueous solution. A little resinous precipitate was removed from the hot solution, and the crystalline precipitate, which separated on cooling, was recrystallised from hot water. There was thus obtained 0·85 gram of a picrate (m. p. 228—229°), which crystallised in bunched, slightly curved, pointed needles. Repeated recrystallisation did not raise the melting point above 233—234°, and analysis showed the salt to be the hitherto undescribed 4(or 5)-β-*aminoethylglyoxaline monopicrate*:

0·0978 gave 0·1396 CO_2 and 0·0282 H_2O. C = 38·8; H = 3·2.

$C_{11}H_{12}O_7N_6$ requires C = 38·8; H = 3·5 per cent.

The monopicrate, on recrystallisation from a large excess of picric acid solution, readily yielded the dipicrate corresponding in all respects with that described by Windaus and Vogt (*loc. cit.*).

4(or 5)-β-*Aminoethylglyoxaline Dihydrobromide.*

The dihydrobromide was prepared by thoroughly shaking the finely powdered dipicrate with ether and a slight excess of dilute hydrobromic acid until all the dipicrate had disappeared. The aqueous solution of the hydrobromide thus obtained was then freed from picric acid by means of ether, digested with a little animal charcoal, filtered, and evaporated to dryness in a vacuum. The residual brown gum became crystalline on the addition of absolute alcohol, and the salt was then purified by recrystallisation from this solvent.

The salt forms stout, colourless, prismatic needles, which melt to a brown liquid at 284° (corr.), after gradually darkening and sintering from about 265°. It is very readily soluble in water, but sparingly so in boiling absolute alcohol. It is anhydrous:

0·1200 gave 0·0957 CO_2 and 0·0440 H_2O. C = 21·7; H = 4·1.

$C_5H_9N_3,2HBr$ requires C = 22·0; H = 4·1 per cent.

(*b*) *At* 240—250°.—Seventy grams of histidine monohydrochloride were heated in sealed tubes with 140 c.c. of 20 per cent. sulphuric acid for three hours at 240—250° in quantities of not more than 4 grams of histidine in one tube; even under these conditions tubes representing 23 grams exploded. The reaction product from the remaining tubes was worked up exactly as described above. There was thus obtained 26·7 grams of a picrate, which melted at 180—190°. On extracting with absolute alcohol, the greater portion dissolved, and the sparingly soluble residue, after recrystallisation from water, gave 4·3 grams of 4(or 5)-β-aminoethylglyoxaline dipicrate. The alcoholic extract was evaporated, and the residue, on crystallisation from water, gave 16·6 grams of pure *r*-histidine dipicrate

r-*Histidine dipicrate* crystallises from water in thin, yellow plates, which contain two molecules of water. After drying at 100°, it begins to sinter at 182°, and decomposes at 190° (corr.). It is readily soluble in alcohol or hot water, but sparingly so in cold water:

0·1660 * lost 0·0091 at 100°. H_2O = 5·5.

$C_{18}H_{15}O_{16}N_9,2H_2O$ requires H_2O = 5·5 per cent.

0·1468 † gave 0·1906 CO_2 and 0·0356 H_2O. C = 35·4; H = 2·7.

0·1364 † „ 24·0 c.c. N_2 at 23° and 766 mm. N = 20·5.

$C_{18}H_{15}O_{16}N_9$ requires C = 35·2; H = 2·5; N = 20·6 per cent.

This salt readily gave the dihydrochloride, which sinters and melts at 225° (corr.): Fränkel (*loc cit.*) gives 220°.

r-*Histidine sesquihydrochloride*, $(C_6H_9O_2N_3)_2,3HCl,H_2O$, crystallises in clusters of flat, prismatic needles when the dihydrochloride is crystallised from dilute alcohol (for instance, when it is dissolved in about twice its weight of water, and four times its weight of alcohol is added). This salt melts at 168—170° (corr.), and suffers no loss in weight at 100°:

0·1513 gave 0·1840 CO_2 and 0·0734 H_2O. C = 33·2; H = 5·4

0·1270 „ 0·1530 CO_2 „ 0·0644 H_2O. C = 32·9; H = 5·7.

---

* Air-dried salt. † Dried at 100°.

0·1570 gave 0·1555 AgCl. Cl = 24·5.
0·1259 ,, 0·1251 AgCl. Cl = 24·6.
$(C_6H_9O_2N_3)_2,3HCl,H_2O$ requires C = 32·9; H = 5·3; Cl = 24·3 per cent.

The composition of this salt is peculiar; there is no evidence of a similar salt of the natural histidine (compare Abderhalden and Einbeck, *Zeitsch. physiol. Chem.*, 1909, **62**, 322).

r-*Histidine monopicrate* crystallises from water in large, flat plates, which are sparingly soluble in hot water and almost insoluble in alcohol. This salt decomposes at 180—181° (corr.), after sintering from about 175°. It contains one molecule of water of crystallisation:

0·3983 * lost 0·0185 at 110°. H_2O = 4·6
$C_{12}H_{12}O_9N_6,H_2O$ requires H_2O = 4·5 per cent.
0·1825 † gave 0·2515 CO_2 and 0·0531 H_2O. C = 37·6; H = 3·3.
$C_{12}H_{12}O_9N_6$ requires C = 37·5; H = 3·2 per cent.

When this salt is dissolved in a hot aqueous solution of picric acid, the dipicrate (m. p. 190°) separates on cooling.

For purposes of comparison, attempts were made to prepare a mono- and di-picrate of naturally occurring histidine. Histidine appears, however, to form only a dipicrate.

Histidine dipicrate crystallises from water in long, flat, clear, well-formed leaflets, which sinter at about 80° and melt at 86° (corr.). It appears to contain two molecules of water:

0·1591 * gave 0·1927 CO_2 and 0·0452 H_2O. C = 33·0; H = 3·2.
$C_{18}H_{15}O_{16}N_9,2H_2O$ requires C = 33·3; H = 3·0 per cent.

The Action of Potassium Hydrogen Suphate on Histidine.

Twenty-five grams of potassium hydrogen sulphate were fused in a beaker heated by an oil-bath and 1 gram of histidine monohydrochloride was added; considerable frothing occurred, and the mixture had to be stirred frequently. After heating for various lengths of time at different temperatures, the reaction product was dissolved in water, neutralised with potassium hydroxide, digested with animal charcoal, cooled, and filtered from charcoal and potassium sulphate. The filtrate was again concentrated, separated from more potassium sulphate, made up to a known volume, and the yield of 4(or 5)-β-aminoethylglyoxaline determined physiologically. Heating at an oil-bath temperature of 260—270° for one hour gave the best yield of the desired base, but the maximum only reached about 5 per cent. of the theoretical. A modification of this method, in which histidine monohydrochloride was heated with ten times its weight of potassium hydrogen sulphate in sealed tubes at 265—270° for three hours, gave yields of 20 to 25 per cent. of the theoretical, as indicated by physiological estimation.

---

* Air-dried salt. † Dried at 110°.

The Formation of 4(or 5)-β-*Aminoethylglyoxaline from Benzoylhistidine.*

Monobenzoylhistidine was prepared by the Schotten-Baumann method, as indicated by Fränkel (*loc. cit.*). It was, however, found to be quite unnecessary to carry out the precipitation with mercuric chloride described by him. On neutralising the solution after the reaction is complete, the pure benzoyl derivative separates very quickly on simply keeping.

One gram of benzoylhistidine so obtained was heated in a vacuum at 240° until all frothing ceased. The black, tarry mass was dissolved in 2 c.c. of concentrated hydrochloric acid, and hydrolysed at 180°. The contents of the tube were washed out with water, and the separated benzoic acid collected, the filtrate extracted with ether, and the aqueous solution neutralised. An equal volume of a solution of picrolonic acid in water was added, and the bulky, amorphous, yellow precipitate collected. The filtrate was concentrated to small bulk, and a concentrated alcoholic solution of picrolonic acid added. After some time, 0·47 gram of 4(or 5)-β-aminoethylglyoxaline picrolonate was obtained, crystallising in bunched needles, and melting at 262—264° (Windaus and Vogt, *loc. cit.*, give "about 266°").

WELLCOME PHYSIOLOGICAL RESEARCH LABORATORIES,
HERNE HILL, S.E.

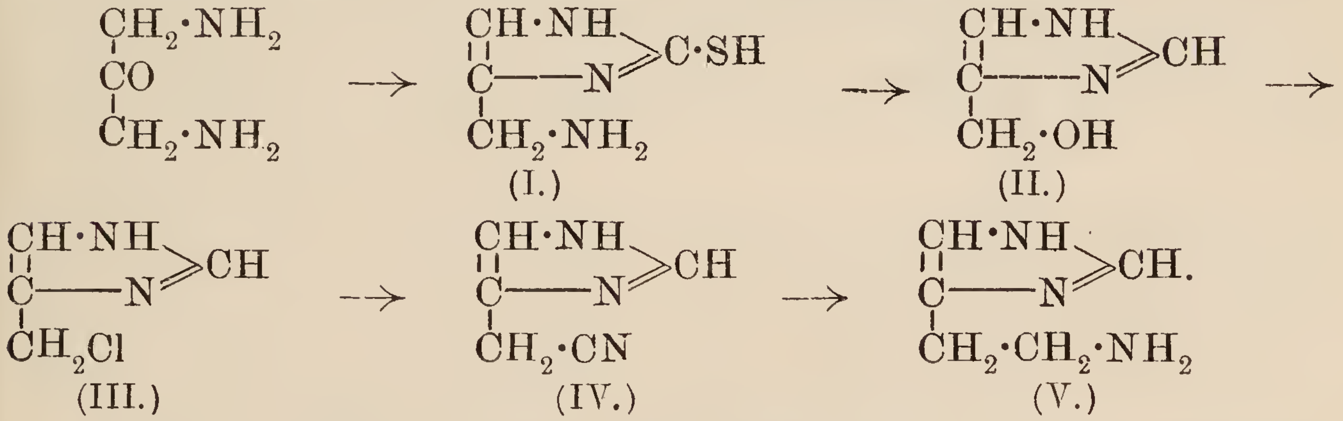
WELLCOME CHEMICAL WORKS,
DARTFORD, KENT.

R. CLAY AND SONS, LTD. BREAD ST HILL, E.C., AND BUNGAY, SUFFOLK

*90. "A new synthesis of 4(or 5)-β-aminoethylglyoxaline, one of the active principles of ergot." By Frank Lee Pyman.

The following synthesis of 4(or 5-)-β-aminoethylglyoxaline affords a convenient method for its preparation.

Diaminoacetone dihydrochloride when heated with potassium thiocyanate yields 2-*thiol*-4(or 5-)-*aminomethylglyoxaline* (I) [m. p. 188° (corr.)], which on oxidation with nitric acid gives 4(or 5)-*hydroxymethylglyoxaline* (II) [m. p. 93—94° (corr.)]. The hydrochloride of the latter is converted by phosphorus pentachloride into 4(or 5)-*chloromethylglyoxaline hydrochloride* (III) [m. p. 144—145° (corr.)], and this, when suitably treated with potassium cyanide, gives rise to 4(or 5)-*cyanomethylglyoxaline* (IV) [m. p. 138—140° (corr.)]. The latter base, on reduction with sodium and alcohol, yields 4(or 5)-β-aminoethylglyoxaline (V).



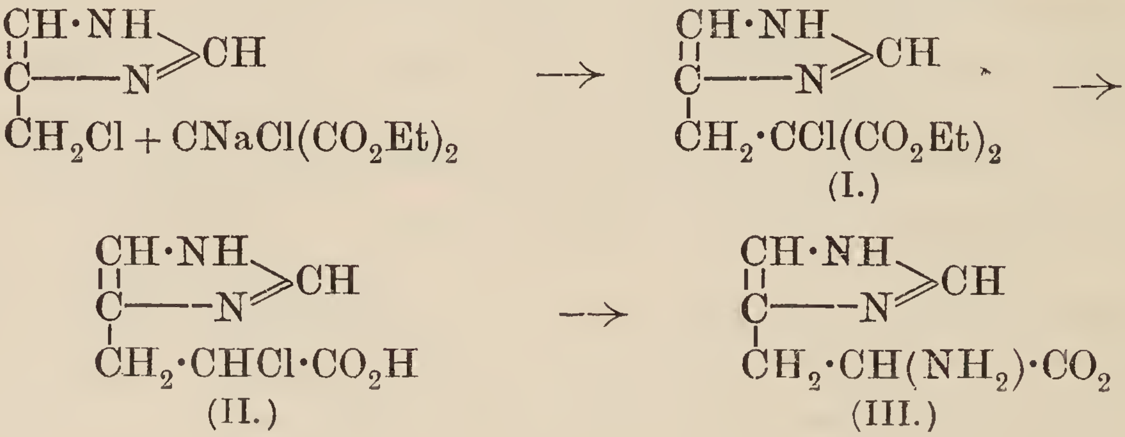
A number of salts of these compounds, and several derivatives obtained as by-products in the various stages of the synthesis, were also described.

*91. "The synthesis of *r*-histidine." (Preliminary note.)

By Frank Lee Pyman.

4(or 5)-Chloromethylglyoxaline hydrochloride, of which the synthetical preparation is described in the preceding communication, is a valuable compound for the synthesis of substances containing the glyoxaline complex, for it reacts readily with ethyl sodioacetoacetate, ethyl sodiomalonate, and similarly constituted compounds, forming the corresponding 4(or 5)-glyoxalinemethyl ($C_3H_3N_2{\cdot}CH_2{-}$) derivatives. By the use of this salt, the synthesis of *r*-histidine has been effected as follows. 4(or 5)-Chloromethylglyoxaline hydrochloride and ethyl sodiochloromalonate readily condense, yielding *ethyl* 4(or 5)-*glyoxalinemethylchloromalonate*

(I), of which the *sesquioxalate*, $(C_{11}H_{15}O_4N_2Cl)_4(C_2H_2O_4)_3$, melts and decomposes at 176° (corr.). This base, on hydrolysis with 20 per cent. hydrochloric acid, gives r-*α-chloro-β-glyoxaline-4*(or 5)-*propionic acid* (II) [m. p. 201° (corr.)], which, when heated with strong ammonia at 110°, yields *r*-histidine (*r*-*α*-amino-*β*-glyoxaline-4(or 5)-propionic acid, (III) [melting and decomposing at 283° (corr.)], identical in all respects with that obtained by racemising the naturally-occurring amino-acid *l*-histidine.



R. CLAY AND SONS, LTD., BREAD ST. HILL, E.C., AND BUNGAY, SUFFOLK.

4

LXXIV.—*A New Synthesis of 4(or 5-)-β-Aminoethylglyoxaline, one of the Active Principles of Ergot.*

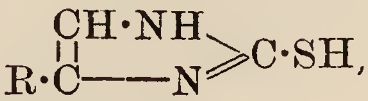
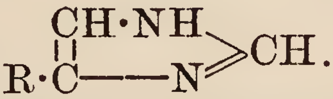
By Frank Lee Pyman.

Barger and Dale (Trans., 1910, **97**, 2592) have recently shown that 4(or 5)-β-aminoethylglyoxaline (β-iminazolylethylamine) occurs in certain aqueous extracts of ergot, and Dale and Laidlaw (*J. Physiol.*, 1910, **41**, 318) have shown that its physiological activity is very great.

This base was first prepared by Windaus and Vogt (*Ber.*, 1907, **40**, 3691), who synthesised it from glyoxaline-4(or 5)-propionic acid through the hydrazide, azide, and urethane by Curtius's method. Glyoxaline-4(or 5)-propionic acid is obtained synthetically only in poor yield by the action of formaldehyde and ammonia on glyoxylpropionic acid (Knoop and Windaus, *Beitr. chem. Physiol. Path.*, 1905, **7**, 144), but may more readily be prepared from the naturally occurring amino-acid histidine (*l*-α-amino-β-glyoxaline-4(or 5)-propionic acid); the latter is, however, a somewhat expensive compound, and 4(or 5)-β-aminoethylglyoxaline is, therefore, not readily accessible by this method.

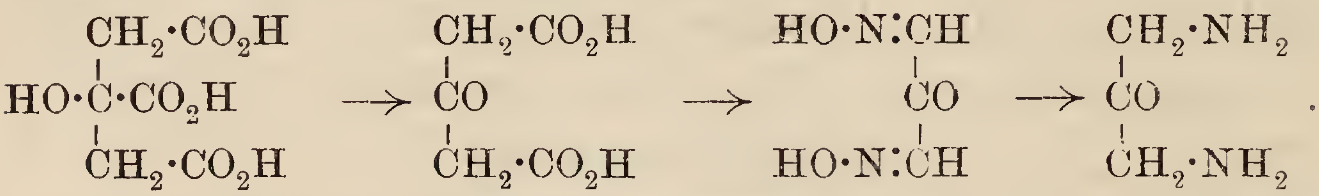
Recently, this base has been prepared directly from histidine by the elimination of carbon dioxide, both by bacterial action (Ackermann, *Zeitsch. physiol. Chem.*, 1910, **65**, 504), and by chemical methods (Ewins and Pyman, this vol., p. 339).

No other method for the preparation of the base has hitherto been described, and its production has, therefore, practically depended on a supply of the naturally occurring amino-acid histidine.

In view of the possible therapeutic importance of this base, it seemed, therefore, important to devise some method by which it could conveniently be synthesised from readily available material, and the following method was found to be suitable. The method is based on Gabriel's discovery (*Ber.*, 1893, **26**, 2204; 1894, **27**, 1037) that amino-ketones of the general formula $R{\cdot}CO{\cdot}CH_2{\cdot}NH_2$ yield, on condensation with potassium thiocyanate, thiolglyoxalines of the general formula  $\begin{matrix}CH{\cdot}NH \\ \| \\ R{\cdot}C\text{——}N\end{matrix}\!\!>C{\cdot}SH$, which may be oxidised by nitric acid to glyoxalines of the type  $\begin{matrix}CH{\cdot}NH \\ \| \\ R{\cdot}C\text{——}N\end{matrix}\!\!>CH$.

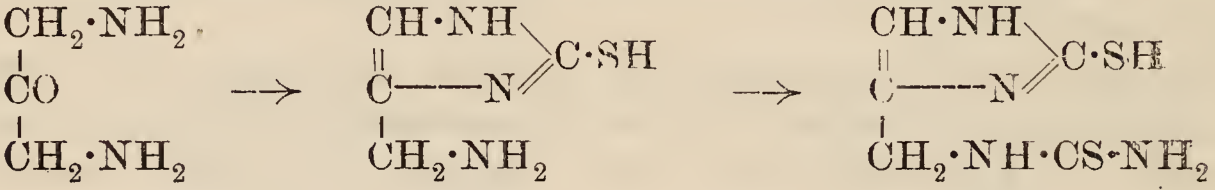
Diaminoacetone dihydrochloride formed the starting material for this synthesis, and this compound is readily prepared from citric acid, through acetonedicarboxylic acid and di*iso*nitrosoacetone by

Kalischer's method (*Ber.*, 1895, **28**, 1519), the course of the reaction being shown by the following scheme:



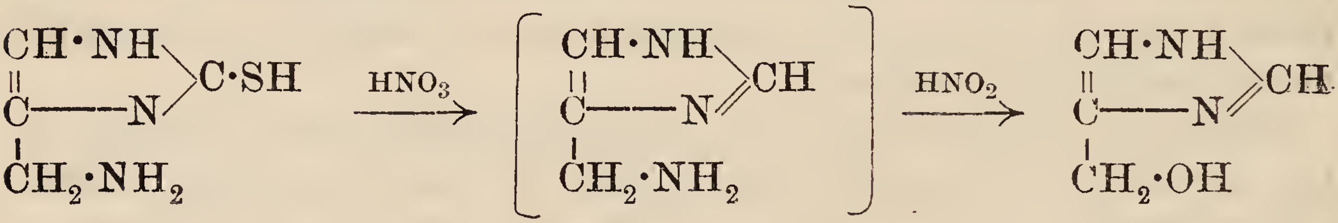
$$\begin{array}{c}CH_2{\cdot}CO_2H\\ |\\ HO{\cdot}C{\cdot}CO_2H\\ |\\ CH_2{\cdot}CO_2H\end{array}\longrightarrow\begin{array}{c}CH_2{\cdot}CO_2H\\ |\\ CO\\ |\\ CH_2{\cdot}CO_2H\end{array}\longrightarrow\begin{array}{c}HO{\cdot}N{:}CH\\ |\\ CO\\ |\\ HO{\cdot}N{:}CH\end{array}\longrightarrow\begin{array}{c}CH_2{\cdot}NH_2\\ |\\ CO\\ |\\ CH_2{\cdot}NH_2\end{array}.$$

Diaminoacetone dihydrochloride, when heated with one molecular proportion of potassium thiocyanate, readily yields 2-*thiol*-4(or 5)-*aminomethylglyoxaline* (I), together with small quantities of 2-*thiol*-4(or 5)-*thiocarbamidomethylglyoxaline* (II):



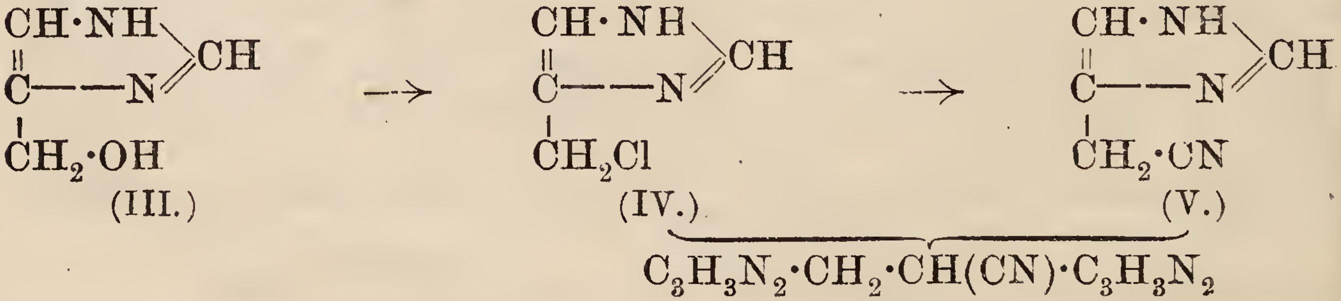
(I.) (II.)

On oxidising the former compound with nitric acid, the thiol sulphur is removed as sulphuric acid, and a glyoxaline results, as in Gabriel's experiments, but the free nitrous acid formed in the reaction attacks the amino-group, replacing it by a hydroxyl group, and the resulting product is 4(or 5)-*hydroxymethylglyoxaline* (III):



(I.) (III.)

The hydrochloride of this base gives with phosphorus pentachloride an excellent yield of the hydrochloride of 4(or 5)-*chloromethylglyoxaline* (IV), and this salt, when dissolved in alcohol and dropped into an ice-cold, saturated aqueous solution of potassium cyanide, gives a 50 per cent. yield of 4(or 5)-*cyanomethylglyoxaline* (V). The latter base, however, is accompanied by a quantity of *αβ-bis*[4(or 5)-*glyoxaline*]-*propionitrile* (VI), besides a considerable quantity of oily by-products, which have not yet been further examined:



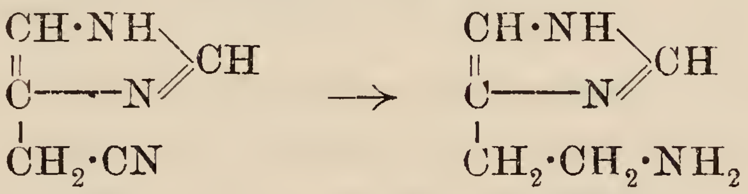
(III.) (IV.) (V.)

$C_3H_3N_2{\cdot}CH_2{\cdot}CH(CN){\cdot}C_3H_3N_2$

(VI.)

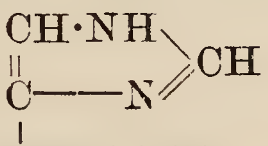
The formation of the last-named compound is, no doubt, due to the condensation of a molecule of the cyano-compound with a molecule of the chloro-compound; it is analogous to the formation of αβ-bis(*o*-nitrophenyl)propionitrile when *o*-nitrobenzyl chloride and potassium cyanide are boiled together for several hours in aqueous alcoholic solution (Bamberger, *Ber.*, 1886, **19**, 2635). The conditions under which the latter reaction takes place are, of course, more severe, and it may be pointed out that in the preparation of phenylacetonitrile from benzyl chloride and potassium cyanide prolonged boiling in aqueous alcoholic solution is also necessary. The extraordinary reactivity of 4(or 5)-chloromethylglyoxaline, indicated by the ease with which the halogen is replaced, emphasises the marked influence of the glyoxaline complex on the side-chain. An attempt was made to effect the replacement of the chloro- by the cyano-group in absolute alcoholic solution, but after several hours' boiling of the hydrochloride of the chloro-compound with finely powdered potassium cyanide in this solvent, a complex mixture was obtained, from which a certain amount of 4(or 5)-*ethoxymethylglyoxaline*, $C_3H_3N_2{\cdot}CH_2{\cdot}OEt$, but none of the cyano-compound, could be isolated.

The last stage of the synthesis of 4(or 5)-β-aminoethylglyoxaline (VII) was accomplished by the reduction of 4(or 5)-cyanomethylglyoxaline by means of sodium and alcohol:

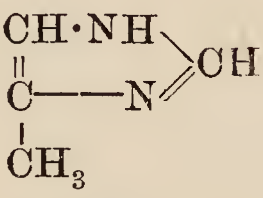


(V.) (VII).

when there were also obtained as by-products a large amount of glyoxaline-4(or 5)-acetic acid (VIII) and a small quantity of 4(or 5)-methylglyoxaline (IX):



(VIII.)



(IX.)

Glyoxaline-4(or 5)-acetic acid, which is thus prepared synthetically for the first time, has previously been obtained by Knoop (*Beitr. chem. Physiol. Path.*, 1907, **10**, 119) by the oxidation of oxydeaminohistidine (α-hydroxy-β-glyoxaline-4(or 5)-propionic acid). It has now been further characterised by the preparation of a number of salts, and its ester, *ethyl glyoxaline*-4(or 5)-*acetate*, has been prepared by the action of alcoholic hydrogen chloride on 4(or 5)-cyanomethylglyoxaline.

The occurrence of 4(or 5)-methylglyoxaline amongst the reduction products of 4(or 5)-cyanomethylglyoxaline is probably due to the loss of carbon dioxide on the part of glyoxaline-4(or 5)-acetic acid.

It was thought possible that the yield of 4(or 5)-β-aminoethylglyoxaline might be increased by converting the cyano-compound into the corresponding thioamide, and reducing this with zinc and dilute hydrochloric acid, a method advantageously employed by Hofmann (*Ber.*, 1868, **1**, 102), and subsequently by Bamberger and Lodter (*Ber.*, 1888, **21**, 51) in the formation of bases of the type $R\cdot CH_2\cdot NH_2$ from cyanides $R\cdot CN$, where R is an aryl radicle; in the present case, however, whilst *glyoxaline*-4(or 5)-*acetthioamide*, $C_3H_3N_2\cdot CH_2\cdot CS\cdot NH_2$, was formed almost quantitatively from 4(or 5)-cyanomethylglyoxaline and alcoholic ammonium sulphide, its reduction led to mere traces of the required product.

In conclusion, it may be mentioned that several of the new glyoxaline derivatives described in this communication form suitable starting points for the synthesis of more complicated substances containing the glyoxaline ring, and it is proposed to attempt the synthesis of such compounds, in particular of those which occur in nature, namely, histidine and pilocarpine.

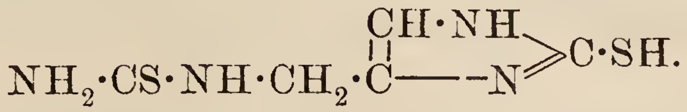
EXPERIMENTAL.

The Action of Potassium Thiocyanate on Diaminoacetone.

Fifty grams of diaminoacetone dihydrochloride were added to a hot solution of 30 grams of potassium thiocyanate in 50 c.c. of water, and the mixture was heated in the steam-bath. At first, a clear solution was obtained, but after about ten minutes crystals began to separate. After heating for about one hour, no further quantity of crystals appeared to be formed, and after heating for another half-hour, the liquor was cooled and the crystals collected (mother liquor *M*). On boiling the crystals with 75 c.c. of water, the bulk passed into solution, but 1·2 grams of 2-*thiol*-4(or 5)-*thiocarbamidomethylglyoxaline*, melting at 233° (uncorr.), remained undissolved, and were collected.

The filtrate was then mixed with a solution of 21 grams of anhydrous potassium carbonate in 75 c.c. of water, somewhat evaporated, and set aside, when 8·2 grams of 2-*thiol*-4(or 5)-*aminomethylglyoxaline*, melting at 188°, separated. To the mother liquor from this crop of crystals the mother liquor *M* was added, and the mixture evaporated to dryness under diminished pressure and extracted with alcohol. After removing the solvent from the alcoholic extract and diluting the resulting dark brown oil with a little water, further crops of nearly pure 2-thiol-4(or 5)-aminomethylglyoxaline, amounting to 17·9 grams, were obtained. The total yield of this base—26·1 grams—represents 64 per cent. of the theoretical.

2-*Thiol*-4(or 5)-*thiocarbamidomethylglyoxaline*,

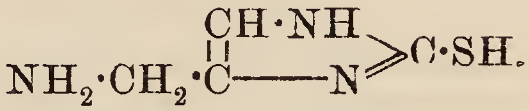


$$\mathrm{NH_2\cdot CS\cdot NH\cdot CH_2\cdot}\begin{array}{l}\mathrm{CH\cdot NH}\\ \Vert \\ \mathrm{C}\text{———}\mathrm{N}\end{array}\!\!>\mathrm{C\cdot SH.}$$

This compound crystallises from boiling water in small, transparent, isolated prisms, which melt and decompose at 237—238° (corr.). It is anhydrous, and is very sparingly soluble in boiling water or alcohol. It is insoluble in dilute hydrochloric acid, but soluble in aqueous sodium hydroxide:

0·1533 gave 0·1807 CO_2 and 0·0607 H_2O. $C=32·1$; $H=4·4$.
$C_5H_8N_4S_2$ requires $C=31·9$; $H=4·3$ per cent.

2-*Thiol*-4(or 5)-*aminomethylglyoxaline*,



$$\mathrm{NH_2\cdot CH_2\cdot}\begin{array}{l}\mathrm{CH\cdot NH}\\ \Vert \\ \mathrm{C}\text{———}\mathrm{N}\end{array}\!\!>\mathrm{C\cdot SH.}$$

This base crystallises from water or alcohol in large, clear, colourless, quadrilateral plates, which melt and decompose at 188° (corr.). It is anhydrous, and is moderately easily soluble in cold water, sparingly so in cold absolute alcohol, but very easily so in hot water. It is sparingly or very sparingly soluble in the other usual organic solvents, even when hot. Aqueous solutions of the base yield with silver nitrate solution a precipitate in the form of a fine, yellow powder, which is not affected by ammonia, but becomes white on the addition of dilute nitric acid; such solutions give a white, amorphous precipitate with aqueous mercuric chloride or a solution of zinc hydroxide in ammonia, and an intense red coloration on the addition of sodium diazobenzene-*p*-sulphonate:

0·1538 gave 0·2079 CO_2 and 0·0783 H_2O. $C=36·9$; $H=5·7$.
0·0744 „ 20·6 c.c. N_2 at 21° and 764 mm. $N=32·3$.
$C_4H_7N_3S$ requires $C=37·2$; $H=5·5$; $N=32·5$ per cent.

The *hydrochloride* crystallises from water in crusts formed by rosettes of needles. This salt darkens at 265°, and is quite charred at 270° (corr.), when it shrinks somewhat, but does not melt. It is anhydrous, and easily soluble in cold water, giving a solution neutral to litmus:

0·1531 gave 0·1647 CO_2 and 0·0685 H_2O. $C=29·3$; $H=5·0$.
0·1615 „ 0·1737 CO_2 „ 0·0735 H_2O. $C=29·3$; $H=5·1$.
$C_4H_7N_3S,HCl$ requires $C=29·0$; $H=4·9$ per cent.

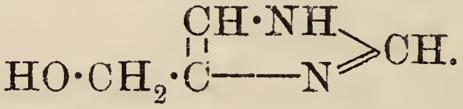
The *picrate* crystallises from water in large, stout, serrated needles of an intense orange colour, which decompose at 237° (corr.). This salt is anhydrous, and is fairly easily soluble in hot water, but very sparingly so in cold:

0·1541 gave 0·1898 CO_2 and 0·0438 H_2O. C = 33·6; H = 3·2.
0·1526 „ 0·1873 CO_2 „ 0·0445 H_2O. C = 33·5; H = 3·2.
$C_4H_7N_3S,C_6H_3O_7N_3$ requires C = 33·5; H = 2·8 per cent.

The Action of Nitric Acid on 2-*Thiol*-4(or 5)-*aminomethylglyoxaline.*

Fifteen grams of 2-thiol-4(or 5)-aminomethylglyoxaline were added gradually during twenty minutes to 300 c.c. of 10 per cent. aqueous nitric acid, which was kept gently boiling over a small flame. The clear, pale yellow liquor was then boiled for ten minutes, neutralised with aqueous sodium hydroxide, and mixed with a solution of 26·6 grams of picric acid in 600 c.c. of boiling water. On cooling, a large quantity of 4(or 5)-*hydroxymethylglyoxaline picrate* separated, and further crops were obtained on concentration. The salt was purified by crystallisation from water, and 27·9 grams of the pure picrate were obtained; the yield thus amounted to 74 per cent. of the theoretical.

4(or 5)-*Hydroxymethylglyoxaline*,



$$\begin{array}{l} \qquad\qquad\quad CH\cdot NH \\ HO\cdot CH_2\cdot C\text{———}N \end{array}\!\!>CH.$$

This base may be obtained from its picrate by shaking the latter with dilute hydrochloric acid and ether until the picric acid is removed, adding to the resulting solution of the hydrochloride an excess of sodium carbonate, evaporating to dryness under diminished pressure, and extracting with absolute alcohol. It crystallises from absolute alcohol in large, clear, colourless hexahedra, which melt at 93—94° (corr.). It is very easily soluble in water, easily so in absolute alcohol, but sparingly so in the other usual organic solvents. It cannot be distilled under 20 mm. pressure, but suffers decomposition:

0·1519 gave 0·2717 CO_2 and 0·0844 H_2O. C = 48·8; H = 6·2.
0·1010 „ 24·6 c.c. N_2 at 22° and 767 mm. N = 28·4.
$C_4H_6ON_2$ requires C = 49·0; H = 6·2; N = 28·6 per cent.

Aqueous solutions of this base give with mercuric chloride, ammoniacal silver nitrate, and ammoniacal solution of zinc hydroxide, white, amorphous precipitates; with sodium diazobenzene-*p*-sulphonate, an intense red coloration.

The *hydrochloride* crystallises from absolute alcohol in long, flat, prismatic needles, which melt at 107—109° (corr.), after sintering from 105°. It is very deliquescent, and very easily soluble in water or alcohol:

0·1542* gave 0·2019 CO_2 and 0·0778 H_2O. C = 35·7; H = 5·7.
0·1383* „ 0·1820 CO_2 „ 0·0702 H_2O. C = 35·9; H = 5·7.

* Dried at 100°.

0·0855* gave 15·3 c.c. N_2 at 18° and 751 mm. N = 20·7.
0·1587* „ 0·1700 AgCl. Cl = 26·5.
$C_4H_6ON_2,HCl$ requires C = 35·7; H = 5·3; N = 20·9;
Cl = 26·3 per cent.

The *nitrate* crystallises from absolute alcohol in wedge-shaped, transparent plates, which melt at 84—86° (corr.), after sintering a few degrees earlier. It is deliquescent, very easily soluble in water or hot absolute alcohol, and easily so in cold absolute alcohol:

0·1399* gave 0·1526 CO_2 and 0·0580 H_2O. C = 29·7; H = 4·6.
$C_4H_6ON_2,HNO_3$ requires C = 29·8; H = 4·3 per cent.

The *picrate* crystallises from water in glistening scales, which melt and decompose at 207° (corr.). It is anhydrous, and is fairly easily soluble in hot water, but very sparingly so in cold:

0·1388 gave 0·1862 CO_2 and 0·0401 H_2O. C = 36·6; H = 3·2.
$C_4H_6ON_2,C_6H_3O_7N_3$ requires C = 36·7; H = 2·8 per cent.

The *hydrogen oxalate* crystallises from water in large, clear, colourless prisms, which contain one molecule of water of crystallisation, and have no sharp melting point, commencing to sinter at 80°, and gradually liquefying between this temperature and 100°. After drying, first at about 50°, then at 100°, this salt melts at 134—136° (corr.). It is soluble in about four parts of cold water, and very easily soluble in hot water:

0·1500† gave 0·1906 CO_2 and 0·0662 H_2O. C = 34·7; H = 4·9.
0·2118† lost 0·0182 at 100°. H_2O = 8·6.
$C_4H_6ON_2,C_2H_2O_4,H_2O$ requires C = 34·9; H = 4·9; H_2O = 8·7
0·1488* gave 0·2072 CO_2 and 0·0545 H_2O. C = 38·0; H = 4·1.
$C_4H_6ON_2,C_2H_2O_4$ requires C = 38·3; H = 4·3 per cent.

The Action of Phosphorus Pentachloride on 4(or 5)-*Hydroxymethylglyoxaline.*

To 57 grams of phosphorus pentachloride contained in a round-bottomed flask, 36·5 grams of 4(or 5)-hydroxymethylglyoxaline hydrochloride were added in small portions, with thorough shaking, in the course of a few minutes. Copious fumes of hydrogen chloride were evolved, and the reaction mass quickly became a viscous liquid, and then solidified. Fifty c.c. of chloroform were then added, to wash any unchanged pentachloride into contact with unchanged hydroxy-compound, and the mixture was then heated on the water-bath, first under ordinary, and then under diminished, pressure to remove chloroform, hydrogen chloride, and phosphoryl chloride. The residue was then dissolved in about

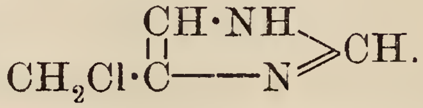
---

* Dried at 100°.

† Air dried salt.

50 c.c. of hot absolute alcohol, and set aside, when 33·0 grams of 4(or 5)-*chloromethylglyoxaline hydrochloride*, melting at 140—142°, separated; on allowing the mother liquor to evaporate spontaneously in a desiccator, a further 2·8 grams of the same salt, in a fairly pure condition, were obtained. The total yield—35·8 grams—amounts to 86 per cent. of the theoretical, and further quantities were obtained by again treating the residual oil with phosphorus pentachloride.

4(or 5)-*Chloromethylglyoxaline*,



$$\begin{array}{l}\qquad\quad\;\mathrm{CH\cdot NH}\\ \mathrm{CH_2Cl\cdot\overset{\|}{C}\text{———}N}\end{array}\!\!>\mathrm{CH}.$$

The *hydrochloride* crystallises from absolute alcohol in prismatic needles or stout prisms, which melt at 144—145° (corr.). This salt is deliquescent, very easily soluble in water or hot absolute alcohol, and fairly easily so in cold absolute alcohol:

0·1531* gave 0·1750 CO_2 and 0·0558 H_2O. C = 31·2; H = 4·1.
0·1539* „ 0·2866 AgCl. Cl = 46·1.
$C_4H_5N_2Cl,HCl$ requires C = 31·4; H = 4·0; Cl = 46·3 per cent.

Aqueous solutions of this salt remain clear on the addition of aqueous sodium carbonate, but become turbid, depositing a yellow oil soluble in excess, on the addition of aqueous sodium hydroxide.

The *picrate* is obtained in long, glistening, silky yellow needles, when a cold solution of picric acid is added to a freshly prepared solution of 4(or 5)-chloromethylglyoxaline hydrochloride in cold water. It is anhydrous, and melts and decomposes at 181° (corr.):

0·1434 gave 0·1810 CO_2 and 0·0334 H_2O. C = 34·4; H = 2·6.
$C_4H_5N_2Cl,C_6H_3O_7N_3$ requires C = 34·7; H = 2·3 per cent.

On dissolving this salt in a little boiling water, and immediately cooling the solution, pure 4(or 5)-hydroxymethylglyoxaline picrate, melting at 207° (corr.), either alone or when mixed with the pure salt, separates.

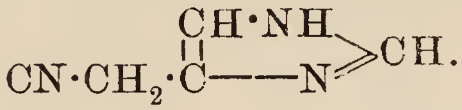
The Action of Aqueous Potassium Cyanide on 4(or 5)-*Chloromethylglyoxaline.*

A solution of 30 grams of 4(or 5)-chloromethylglyoxaline hydrochloride in 135 c.c. of absolute alcohol was added drop by drop to 90 grams of potassium cyanide in 100 c.c. of water, which was mechanically stirred and kept at about 0°, the addition occupying approximately thirty minutes. The mixture was then filtered, and the potassium salts washed with alcohol. The filtrate and washings were combined, mixed with 180 c.c. of 10 per cent. aqueous sodium carbonate, and evaporated to dryness under diminished pressure. The residue was extracted with warm ethyl acetate, and the extract distilled, when 16·3 grams of a brown oil remained. This began to crystallise, and after dissolution in a little warm water, 7·5 grams of pure 4(or 5)-*cyanomethylglyoxaline* separated, and a second crop of 1·0 gram of the cyano-base was obtained on concentrating the mother liquor. The oily liquor remaining was then converted into the acid oxalate by the addition of 9 grams of oxalic acid, and the resulting crops of mixed oxalates fractionally crystallised from water, when small quantities of 4(or 5)-cyanomethylglyoxaline acid oxalate and *αβ-bis*[4(or 5)-*glyoxaline*]-*propionitrile hydrogen oxalate* were obtained. These oxalates, however, readily crystallise out side by side, and their separation is tedious. The total yield of 4(or 5)-cyanomethylglyoxaline amounts to about 50 per cent. of the theoretical.

---

* Dried at 100°.

4(or 5)-*Cyanomethylglyoxaline*,



$$\begin{array}{l} \qquad\qquad\;\; \mathrm{CH{\cdot}NH} \\ \qquad\qquad\;\; \| \qquad\qquad > \mathrm{CH.} \\ \mathrm{CN{\cdot}CH_2{\cdot}C}\text{——}\mathrm{N} \end{array}$$

This base crystallises from water or ethyl acetate in stout, prismatic needles, which sinter at 136°, soften at 137°, and melt to a clear liquid at 138—140° (corr.). It is sparingly soluble in ether, chloroform, benzene, light petroleum, or cold water, but easily so in ethyl acetate, acetone, alcohol, or hot water:

0·1339 gave 0·2755 CO_2 and 0·0573 H_2O. $C=56{\cdot}1$; $H=4{\cdot}8$.
0·0673 „ 22·5 c.c. N_2 at 19° and 770 mm. $N=39{\cdot}6$.
$C_5H_5N_3$ requires $C=56{\cdot}0$; $H=4{\cdot}7$; $N=39{\cdot}2$ per cent.

Aqueous solutions of this base give with mercuric chloride, ammoniacal silver nitrate, and ammoniacal solution of zinc hydroxide, white, amorphous precipitates; with sodium diazobenzene-*p*-sulphonate, a dirty brownish-red colour, very much more intense than the beautiful red colour given by other glyoxalines containing a free imino-hydrogen atom, is produced; the difference is probably due to the product containing two chromophoric groups, one of which is attached to the imino-group as in other glyoxalines, and the second to the methylene group which is situated between the glyoxaline complex and the cyano-group.

The *hydrochloride* crystallises from absolute alcohol in thin, glistening leaflets, which melt at 168—169° (corr.). It is very easily soluble in water, and fairly easily so in boiling absolute alcohol, but sparingly so in the latter when cold:

0·1514 gave 0·2315 CO_2 and 0·0585 H_2O. $C=41{\cdot}7$; $H=4{\cdot}3$.
$C_5H_5N_3,HCl$ requires $C=41{\cdot}8$; $H=4{\cdot}2$ per cent.

The *hydrogen oxalate* crystallises from water in crusts consisting of indefinite prisms. This salt decomposes at 194° (corr.), and is easily soluble in hot water, but sparingly so in cold:

0·1542 gave 0·2403 CO_2 and 0·0546 H_2O. C = 42·5; H = 4·0.
$C_5H_5N_3,C_2H_2O_4$ requires C = 42·6; H = 3·6 per cent.

The *picrate* crystallises from water in yellow leaflets, which begin to sinter at 155°, and melt at 165—166° (corr.). It is sparingly soluble in cold water or alcohol.

$\alpha\beta$-Bis[4(or 5)-*Glyoxaline*]-*propionitrile*, $C_3H_3N_2{\cdot}CH_2{\cdot}CH(CN){\cdot}C_3H_3N_2$.

The *hydrogen oxalate* crystallises from water in stout, clear, prismatic needles, which melt and decompose at 181—182° (corr.). It is anhydrous and somewhat sparingly soluble in cold water, but easily so in hot water:

0·1528 gave 0·2288 CO_2 and 0·0477 H_2O. C = 40·8; H = 3·5.
0·1052 „ 15·2 c.c. N_2 at 18° and 769 mm. N = 17·2.
$(C_9H_{10}N_5)_2,5C_2H_2O_4$ requires C = 40·7; H = 3·7; N = 17·0;
$C_2H_2O_4$ = 54·5 per cent.

On dissolving 2·05 grams of this salt in water, and adding an excess of barium hydroxide solution, 2·8 grams of barium oxalate, corresponding with 54·6 per cent. of oxalic acid were collected; the filtrate from this, after treatment with carbon dioxide and removal of barium carbonate, was evaporated to dryness, when a colourless varnish remained. This was readily soluble in water, giving an alkaline solution, and when acidified with hydriodic acid and evaporated to low bulk, gave a beautifully crystalline hydriodide.

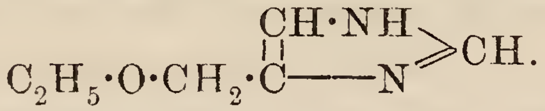
The *hydriodide* crystallises from water in well-formed rhombic prisms, which melt at 200—201° (corr.). It is sparingly soluble in cold water or alcohol, and is anhydrous:

0·1539 gave 0·1932 CO_2 and 0·0467 H_2O. C = 34·2; H = 3·4.
0·1472 „ 27·4 c.c. N_2 at 14° and 768 mm. N = 22·4.
0·2030 „ 0·1496 AgI. I = 39·8.
$C_9H_{10}N_5,HI$ requires C = 34·2; H = 3·5; N = 22·2; I = 40·1 per cent.

The Action of Alcoholic Potassium Cyanide on 4(or 5)-*Chloromethylglyoxaline.*

Ten grams of 4(or 5)-chloromethylglyoxaline hydrochloride, 12 grams of finely powdered potassium cyanide, and 40 c.c. of absolute alcohol were boiled together under a reflux condenser for five and a-half hours. The mixture was then filtered from the potassium salts, and these washed with alcohol; the filtrate was rendered alkaline with 80 c.c. of 10 per cent. aqueous sodium carbonate, and evaporated to dryness under diminished pressure. The residue was thoroughly extracted with ether, and gave 5·6 grams of pale yellow oil; this was mixed with its own weight of oxalic acid, and the acid oxalates fractionally crystallised from water, when 3·4 grams of pure 4(or 5)-*ethoxymethylglyoxaline hydrogen oxalate* were obtained; besides this oxalate, which separates first in large crystals, other crystalline oxalates were present in the mother liquors. No 4(or 5)-cyanomethylglyoxaline hydrogen oxalate could be isolated from them by fractional crystallisation, and they were not further examined.

4(or 5)-*Ethoxymethylglyoxaline*,



$$C_2H_5\cdot O\cdot CH_2\cdot \overset{CH\cdot NH}{\overset{\|}{C}}\text{——}N \gtrdot CH.$$

This base is liberated from the oxalate by treating the latter with baryta, filtering from barium oxalate, and removing the excess of baryta as carbonate. It crystallises from anhydrous ether in prismatic needles, which sinter from 50°, and melt at 53—55° (corr.).

It is easily soluble in water, and the usual organic solvents, with the exception of light petroleum:

0·1530 gave 0·3219 CO_2 and 0·1097 H_2O. C = 57·4; H = 8·0.
0·1533 „ 0·3199 CO_2 „ 0·1094 H_2O. C = 56·9; H = 8·0.
$C_6H_{10}ON_2$ requires C = 57·1; H = 8·0 per cent.

The *hydrogen oxalate* crystallises from water in large prisms, which melt at 165—167° (corr.). It is anhydrous, and is soluble in about 4 parts of cold water, but readily so in hot water:

0·1563 gave 0·2668 CO_2 and 0·0839 H_2O. C = 46·6; H = 6·0.
0·1443 „ 0·2457 CO_2 „ 0·0794 H_2O. C = 46·4; H = 6·2.
0·1274 „ 16·0 c.c. N_2 at 21° and 754 mm. N = 14·5.
$(C_6H_{10}ON_2)_4,(C_2H_2O_4)_3$ requires C = 46·5; H = 6·0; N = 14·6 per cent.

The Reduction of 4(or 5)-*Cyanomethylglyoxaline. Preparation of* 4(or 5)-*β-Aminoethylglyoxaline.*

Ten grams of 4(or 5)-cyanomethylglyoxaline were dissolved in 50 c.c. of absolute alcohol, and 25 grams of sodium added piece by piece within a few minutes. Further quantities of hot absolute alcohol were added a few c.c. at a time, while the mixture was heated by a small flame, until after the addition of about 200 c.c. of absolute alcohol (making 250 c.c. in all) in the course of an hour and a-quarter, nearly all the sodium had dissolved. A little water was then added to remove the last traces of sodium, and the liquor was acidified by the addition of 120 c.c. of concentrated hydrochloric acid. After removing the sodium chloride, and washing this with alcohol, the filtrate was evaporated to low bulk, mixed with 100 c.c. of cold saturated aqueous sodium carbonate, and evaporated to complete dryness under diminished pressure. The residue was then extracted with absolute alcohol, which removed all the organic matter, and the extract was concentrated to about 50 c.c., when, on cooling, 4·65 grams of crude *sodium glyoxaline-4(or 5)-acetate* were deposited as a crystalline powder, which was collected, washed with absolute alcohol, and reserved. The alcoholic mother liquor left on evaporation about 8 grams of a viscid brown oil. This was dissolved in a little water, and added to a boiling solution of 30 grams of picric acid in one litre of water. On cooling, a quantity of 4(or 5)-β-aminoethylglyoxaline dipicrate crystallised out, mixed with a little dark brown resinous matter; after recrystallisation from water, the latter was removed, and 14·6 grams of pure dipicrate were obtained.

4(or 5)-β-Aminoethylglyoxaline dipicrate, either alone or mixed with the salt prepared from histidine (Ewins and Pyman, *loc. cit.*), melted and decomposed at 238—242° (corr.), according to the rate of heating:

0·1487 gave 0·1946 CO_2 and 0·0375 H_2O. C = 35·7; H = 2·8.
$C_5H_9N_3,(C_6H_3O_7N_3)_2$ requires C = 35·8; H = 2·7 per cent.

It was further identified by converting it into the dihydrobromide which melted and decomposed at 284° (corr.):

0·1541 gave 0·1232 CO_2 and 0·0578 H_2O. C = 21·8; H = 4·2.
$C_5H_9N_3,2HBr$ requires C = 22·0; H = 4·1 per cent.

Dr. P. P. Laidlaw, of the Wellcome Physiological Research Laboratories, kindly tested a specimen of this synthetic 4(or 5)-β-aminoethylglyoxaline dipicrate, and found that it had the physiological activity of the pure salt prepared from histidine.

After the separation of the dipicrate, the mother liquors deposited first a crystalline picrate, melting at about 160—170°, and then a sticky oil; these fractions, on extraction with a little warm alcohol, gave 0·6 gram of 4(or 5)-β-aminoethylglyoxaline dipicrate as a sparingly soluble residue. This was collected, and all the picrate mother liquors—alcoholic and aqueous—were then combined and boiled to remove the alcohol. The clear hot solution was mixed with concentrated hydrochloric acid, cooled, filtered from picric acid, and extracted with ether to remove the remainder of the latter. The resulting solution of hydrochlorides was made alkaline with sodium carbonate, evaporated to complete dryness under diminished pressure, and extracted first with ether, then with absolute alcohol.

From the ethereal extract, 1·0 gram of nearly colourless, viscid oil was obtained. This was converted into the picrate, and crystallised first from water, then from alcohol, when 1·35 grams of pure 4(or 5)-methylglyoxaline picrate were isolated. This salt melted at 160—162° (corr.), both alone and when mixed with the salt prepared from the pure base; the latter salt had the same melting point. Windaus and Knoop (*Ber.*, 1905, **38**, 1170) give 159—160°:

0·1471 gave 0·2074 CO_2 and 0·0397 H_2O. C = 38·5; H = 3·0.
0·1028 „ 19·4 c.c. N_2 at 13° and 775 mm. N = 23·0.
$C_4H_6N_2,C_6H_3O_7N_3$ requires C = 38·6; H = 2·9; N = 22·5 per cent.

The alcoholic extract left, on evaporation, 1·2 grams of crude crystalline sodium 4(or 5)-glyoxaline acetate; this was combined with the 4·65 grams which had separated earlier, neutralised with hydrochloric acid, and converted into the picrate, when 11·5 grams of pure glyoxaline-4(or 5)-acetic acid picrate, melting at 212—213° (corr.), were obtained. The yield of 4(or 5)-β-aminoethylglyoxaline —15·2 grams of the dipicrate—amounts to 29 per cent., and that of glyoxaline-4(or 5)-acetic acid to 35 per cent., of the theoretical.

Glyoxaline-4(or 5)-*acetic Acid*, $C_3H_3N_2{\cdot}CH_2{\cdot}CO_2H$.

This substance was obtained by treating its hydrochloride with silver carbonate, filtering from silver chloride, removing the excess of silver present as glyoxalineacetate by means of hydrogen sulphide, and concentrating the liquor to low bulk, when it separated in fan-shaped clusters of prismatic needles, which melt and decompose at 222° (corr.):

0·1613 lost 0·0201 at 100°. H_2O = 12·5.
$C_5H_6O_2N_2,H_2O$ requires H_2O = 12·5 per cent.
0·1412 gave 0·2466 CO_2 and 0·0600 H_2O. C = 47·6; H = 4·8.
$C_5H_6O_2N_2$ requires C = 47·6; H = 4·8 per cent.

This acid has previously been prepared by Knoop (*Beitr. chem. Physiol. Path.*, 1907, **10**, 111) by the oxidation of oxydeaminohistidine, that is, α-hydroxy-β-glyoxaline-4(or 5)-propionic acid, $C_3H_3N_2{\cdot}CH_2{\cdot}CH(OH){\cdot}CO_2H$. He describes it as fan-shaped needles from aqueous acetone, which contain $1H_2O$, and melt and decompose at 220°.

The *hydrochloride* crystallises from absolute alcohol in small needles, which melt and decompose at 225—226° (corr.), after sintering a few degrees earlier. It is anhydrous, and is very easily soluble in water, but sparingly so in alcohol:

0·1541 gave 0·2080 CO_2 and 0·0618 H_2O. C = 36·8; H = 4·5.
0·2002 „ 0·1767 AgCl. Cl = 21·8.
$C_5H_6O_2N_2,HCl$ requires C = 36·9; H = 4·4; Cl = 21·8 per cent.

The *picrate* crystallises from hot water in handsome yellow plates, which melt at 212—213° (corr.). It is anhydrous and easily soluble in hot water or alcohol, but sparingly so in these solvents when cold:

0·1515 gave 0·2044 CO_2 and 0·0371 H_2O. C = 36·8; H = 2·7.
0·0830 „ 13·5 c.c. N_2 at 13° and 773 mm. N = 19·7.
$C_5H_6O_2N_2,C_6H_3O_7N_3$ requires C = 37·2; H = 2·6; N = 19·8 per cent.

Sodium glyoxaline-4(or 5)-*acetate* crystallises from absolute alcohol in small needles containing half a molecular proportion of water of crystallisation, which is retained at 100°, but lost at 120°. This salt is very easily soluble in water, and fairly easily so in hot absolute alcohol:

0·1633 * lost 0·0087 at 120°. H_2O = 5·3.
0·2144 * gave 0·0955 Na_2SO_4. Na = 14·4.
$C_5H_5O_2N_2Na,\frac{1}{2}H_2O$ requires Na = 14·6; H_2O = 5·8 per cent.
0·1546 † gave 0·0724 Na_2SO_4. Na = 15·2.
$C_5H_5O_2N_2Na$ requires Na = 15·5 per cent.

Ethyl Glyoxaline-4(or 5)-*acetate*, $C_3H_3N_2\cdot CH_2\cdot CO_2Et$.

Five grams of 4(or 5)-cyanomethylglyoxaline were dissolved in 25 c.c. of absolute alcohol, and a stream of dry hydrogen chloride passed through the solution while boiling gently. After two or three minutes, ammonium chloride began to separate out, and after ten minutes, this was removed by filtration. The liquor was evaporated almost to dryness under diminished pressure, and the sticky residue dissolved in about 30 c.c. of hot acetone, when, on cooling, crude ethyl glyoxaline-4(or 5)-acetate hydrochloride separated. After recrystallisation from acetone, 4·2 grams of this salt were obtained in a pure state, and the mother liquors contained more of this salt mixed with glyoxaline-4(or 5)-acetic acid hydrochloride.

Ethyl glyoxaline-4(or 5)-*acetate hydrochloride* crystallises from acetone in clusters of prismatic needles, which melt at 115—117° (corr.). It is deliquescent, very easily soluble in water or alcohol, fairly easily soluble in hot, but sparingly so in cold, acetone:

0·1538 * gave 0·2471 CO_2 and 0·0803 H_2O. C = 43·8; H = 5·9.
$C_7H_{10}O_2N_2,HCl$ requires C = 44·1; H = 5·8 per cent.

The free base may be isolated as a colourless oil by mixing the hydrochloride with a slight excess of 10 per cent. aqueous sodium carbonate, evaporating to dryness in a vacuum, and extracting with ethyl acetate.

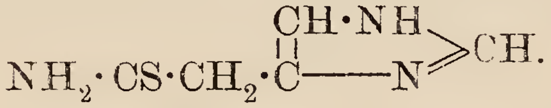
---

* Dried at 100°. † Dried at 120°.

The *hydrogen oxalate* crystallises from water in large prisms, which melt and decompose at 180° (corr.), after sintering a few degrees earlier. It is anhydrous, and is easily soluble in water, but sparingly so in alcohol:

0·1503 gave 0·2443 CO_2 and 0·0665 H_2O. $C=44·3$; $H=5·0$.
$C_7H_{10}O_2N_2,C_2H_2O_4$ requires $C=44·2$; $H=5·0$ per cent.

Glyoxaline-4(or 5)-*acet-thioamide*,



$$\begin{array}{l} \qquad\qquad\qquad\quad CH\cdot NH \\ \qquad\qquad\qquad\quad \| \\ NH_2\cdot CS\cdot CH_2\cdot C\text{——}N \end{array} > CH.$$

Three grams of 4(or 5)-cyanomethylglyoxaline were dissolved in 30 c.c. of alcohol, mixed with 30 c.c. of a cold saturated alcoholic solution of ammonium sulphide, and kept overnight at 40° in a closed vessel. On distilling off the greater part of the alcohol under diminished pressure, the thio-derivative crystallised from the residual liquor while still warm, and 2·5 grams of the pure substance in the form of a nearly white, crystalline powder were obtained in the first crop, and further small quantities subsequently.

Glyoxaline-4(or 5)-*acet-thioamide* crystallises well from water in prisms, and from absolute alcohol in rosettes of needles. On heating, it darkens slightly from about 140°, and considerably from 160°, and eventually melts and decomposes at 173° (corr.). It is easily soluble in hot water, fairly easily so in hot absolute alcohol, and sparingly so in these solvents when cold. It is anhydrous:

0·1543 gave 0·2419 CO_2 and 0·0703 H_2O. $C=42·8$; $H=5·1$.
$C_5H_7N_3S$ requires $C=42·5$; $H=5·0$ per cent.

On reducing 1 gram of this base with zinc dust and dilute hydrochloric acid in cold alcoholic solution for several days, and working up the reaction product for 4(or 5)-β-aminoethylglyoxaline, only about 0·05 gram of the dipicrate of this base was obtained.

Wellcome Chemical Works,
Dartford, Kent.

R CLAY AND SONS. LTD., BREAD STREET HILL, E.C., AND BUNGAY, SUFFOLK